NUTRITION
AND
ATHEROSCLEROSIS

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Preface

This book is based on the 1956 Henry Jackson Lecture of the New England Cardiovascular Society, given by one of us (L. N. K.) in Boston on May 14, 1956. In reviewing the original manuscript, it was decided to undertake its expansion into a comprehensive review and appraisal of the rapidly developing field of atherosclerosis research. This review of the literature was undertaken primarily by one of us (J. S.). In addition, newer data from our own studies have been incorporated. For the documentation of this evaluation, attention was given principally to the newer data since previous reviews had covered the earlier literature in detail (1, 8, 9, 12, 13, 645). For this reason, the bibliography is in the main made up of references since 1953.

As a result of this review and of our own work to date, we have presented some positive practical suggestions for prophylaxis and therapy in this book. This is an active, positive approach to this disease problem and is in marked contrast to the therapeutic nihilism of only a few years ago. It is an approach fully consonant with the recent advances and the present day status of our knowledge in this field. It is, in our opinion, the only sound conclusion to a review of progress in this research area—for the progress has indeed been formidable—although the work is as yet unfinished.

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Jeremiah Stamler
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Acknowledgments

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In the investigation of the possible efficacy of estrogens in the long term therapy of coronary heart disease in middle aged males acknowledgment is gratefully expressed to Dr L A Baker Chief of Medicine, Hines Veterans Administration Hospital Hines Illinois who made a decisive contribution in enlisting the *cooperation of the several participating* Veterans Administration Hospitals in the Midwest Dr B Kaplan has also made a major contribution throughout latterly he and Dr A Pick have served as clinical coordinators of the entire study This research *endeavor has proceeded only* by virtue of the conjoint efforts of members of the medical staffs at several Veterans Administration Hospitals including Drs J Berry D T Foxworthy E Kaplan and W R O Connor Hines Hospital Hines Illinois, Drs R Eckhart C Pilz and H Zimmerman West Side Hospital Chicago Illinois Drs R E Reichert Jr and J A Wood, Ann Arbor Michigan Drs A P Klotz and W E Larsen Kansas City Missouri Drs M Armstrong W E Connor and W M Kirkendall Iowa City Iowa Drs L J Baer and M R Weed, Dearborn Michigan Drs M W Garry and G Spencer Wood Hospital Milwaukee Wisconsin Drs G Fischer and R Gieselman St Louis

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Contents

Chapter 1

Introduction

Atherosclerosis together with hypertension is the most important pathologic process producing morbidity and mortality in the United States today It is present in the coronary arteries of a majority of American males over 25 years of age (290–292 294, 300) It produces

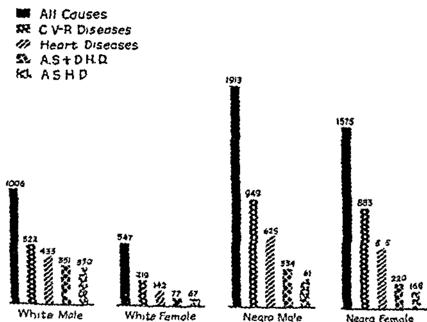


Fig 1 Stamler J (?3) Death rates (at top of column) in this and subsequent figures are per 100 000 population Note that arteriosclerotic heart disease (A S H D — category 470 in the International Statistical Classification of Diseases and Causes of Death [I S C]) and arteriosclerotic and degenerative heart disease (A S and D H D — categories 470 + 472 in the I S C) account for approximately one third of all deaths among white males age 45–54 Note the marked sex differential in A S H D mortality rates of the Negro mortality patterns (see text) The category C V R diseases is the broad grouping of the cardiovascular renal diseases

disease at epidemic rates, thus, the annual incidence rate for coronary heart disease is approximately 1,000 cases per 100,000 males age 45 to 64 (2) It is the number one killer, not only of the elderly, but also of the middle aged (particularly men) in the prime of life (Fig 1) (23) The current research emphasis on this scourge is, therefore, highly in order

The intensive investigations of recent years have shed light particularly on the relationships of dietary patterns and endogenous (especially hormonal) factors to the etiology and pathogenesis of morphologic atherosclerosis and clinical atherosclerotic disease (1, 3–9, 12–23, 71, 171 645, 646) Their findings have led to the elaboration of important theoretical concepts which integrate present knowledge, point the way to further study, and presage effective prophylaxis and therapy This monograph is a review of recent research in these two major areas, including a summation of our group's work during this period It attempts to delineate the inter relationships between dietary and endogenous factors in the etiology and pathogenesis of atherosclerosis On this basis it arrives at an evaluation of the current status of the problem of nutrition and atherosclerosis

Chapter 2

Nutrition and Atherosclerosis

A The Nutritional Metabolic Cholesterol-Lipid-Lipoprotein Theory of Atherogenesis

In previous reports detailed factual and conceptual elaboration was presented of the nutritional metabolic cholesterol lipid lipoprotein theory of atherogenesis (1, 12–23, 645) The basic ideas may be briefly summarized as background for examining the specific problem of the relationship *between diet and atherosclerosis Atherosclerosis is a distinct* entity It is one among the arterioscleroses by far the most important (1) It is a process separate and different from—but intertwined with—hypertension Atherosclerosis is the chief pathologic lesion in coronary heart disease (290–292 294, 297–299) It is a disease Therefore, it is not inevitable nor is it irreversible Rather it is preventable and (at least up to a point) curable

Further atherosclerosis is a metabolic disease in which altered cholesterol lipid lipoprotein metabolism plays a critical and decisive (but not exclusive) role Elevated levels of circulating plasma cholesterol lipids-lipoproteins are cardinal signs of this metabolic abnormality and constitute the metabolic prerequisites for atherogenesis in most persons afflicted during middle-age Without such lipid metabolic derangements clinically significant atherosclerosis would rarely occur in middle age regardless of the functional status of the cardiovascular system and the organism as a whole

Finally—and this is the decisive point in terms of the problem of the relationship between diet and atherosclerosis—the atherogenic alterations in cholesterol lipid lipoprotein metabolism are frequently brought about by the life span pattern of diet They are byproducts of an habitually unbalanced diet excessive in total calories empty calories total fats *saturated fats cholesterol refined carbohydrates* salt and inadequate (relatively and/or absolutely) in certain essential nutrients (vitamins minerals essential amino acids and essential fatty acids) and in bulk Empty calories are calories derived from processed refined foods high in energy value and low in essential nutrients (minerals vitamins essential amino acids and essential fatty acids)—foods such as sugar, white

flour breads and pastries, solid cooking and table fats, and many others (16 64)

These concepts concerning the interrelationships among diet, cholesterol lipid lipoprotein metabolism and atherogenesis are documented by abundant data accumulated by the three major investigative approaches to the problem—the epidemiologic, the clinical pathologic and the animal experimental methods of research

Let us examine the evidence from each

B The Epidemiologic Method

The epidemiologic approach (23–32) is essentially demographic and ecologic in orientation focussing on populations and occurrence of disease in them—in contrast to the clinical approach which concentrates on individual patients and groups of sick people irrespective of the populations-at large from which they originate Epidemiologic research is based on the premise that important leads to the etiology of disease may be obtained by getting answers to such questions as Does the incidence of coronary heart disease vary in time and space—and if so, why? Is it greater today than 50 years ago—and if so, why? Is it greater in some countries than in others—and if so why? Is it greater among males or females, urban or rural dwellers, whites or Negroes, rich or poor, manual (blue collar) or white collar workers—and if there are differences, or similarities in incidence between such groups why?

The significance of the *why is that it may give leads to the etiology of disease*—it is not enough merely to delineate group trends in incidence of disease Once patterns of incidence are defined, it becomes essential to proceed to the decisive questions What accounts for observed differences or similarities? What is the role of diet occupation physical activity, smoking climate income housing, mores tensions stresses, race ethnic origin heredity genetics and other factors? And what are the mechanisms whereby specific causative factors operate?

Obviously the complex questions posed by the epidemiologic method can be fruitfully clarified only by extensive cross fertilization among many disciplines (sociology anthropology nutrition psychology genetics, and others) and by close coordination among medical investigators utilizing the clinical pathologic animal experimental and epidemiologic approaches

C Human Nutrition—Historical and Ecological Background

The relationship between diet and atherosclerosis is best understood against the background of certain cardinal facts concerning human nutrition In terms of man s phylogenesis biological and sociological contemporary American patterns of diet represent relatively recent innovations in nutrition They are diets markedly different in composition

qualitatively and quantitatively, from any ever consumed by wild animals or most pre literate peoples (12, 13, 33) These nutritional patterns are relatively recent products of a long and complex development In terms of the time scale of human evolution their origins go back only about 8,000 years Prior to that time man had been exclusively a food gatherer He had not yet learned to be a food producer Inevitably therefore his eating habits differed markedly from ours (33) Composed of a variety of natural unprocessed foods yielding a high ratio of essential nutrients to calories his diets were invariably very nourishing and well balanced (as long as nature's bounty was adequate) This was true irrespective of their specific patterns, reflective of given local conditions (32–34)

In the Fertile Crescent of the Middle East man made the decisive historic leap from food gathering to food producing and became a farmer and a herder This Neolithic transition created the economic pre-conditions for urban life (35–37) It also made available for the first time many of the foods commonly consumed by most Americans today, *e g* dairy products, eggs cereals breads, and other foods (33)

The historic record clearly reveals that the privileged classes in the ancient empires soon learned to enjoy rich "luxus' diets very much like our own This was true of the Egyptian nobility and priesthood—whose mummies reveal bits of aorta with gross atherosclerosis (32) In the words of the Biblical scribes they lived 'off the fat of the land ' (38 39)

The bulk of the population however subsisted on very different far simpler fare in Egypt of the Pharaohs it was bread and beer (32) From ancient times right down to the present bread—with rice and potatoes—has been the staff of life ' For the majority of mankind—particularly in economically underdeveloped Africa Asia Latin America eastern and southern Europe—grains have remained the chief staples supplying 60 to 90 per cent of daily calories (Fig 2) (40–63)

Unquestionably people on such diets are not well provided for nutritionally (66) Many of them suffer from permanent malnutrition—more precisely *undernutrition*

In the economically developed countries a marked change in nutritional patterns has occurred during the last century In conjunction with industrialization urbanization and increase in per capita national income richer diets have become commonplace—diets containing sizable quantities of the more expensive high lipid foods of animal origin (well fattened meats eggs butter and other dairy products) plus elegant' white bread and refined sugar These foods are now consumed *en masse* in countries like the United States As a result intake *en masse* of total calories empty calories total fats cholesterol saturated fats has tended to increase significantly in these economically developed countries It should be stressed that the rise in total fat intake is almost exclusively

attributable to the increased ingestion of *saturated* fats of animal origin (*not* unsaturated vegetable and marine oils) It is quite exceptional to find a sizable population consuming a high level of fat, *e g* 30 to 40 per cent of total calories, derived chiefly from vegetable sources, *i e* mainly unsaturated fat (*cf* 67, 139, 167, 251) This evolutionary change in dietary habits has been repeatedly observed, as virtually an invariable concomitant of improved economic conditions (40–45, 63, 65–67)

DIET IN MORE DEVELOPED AND
LESS DEVELOPED COUNTRIES-1950

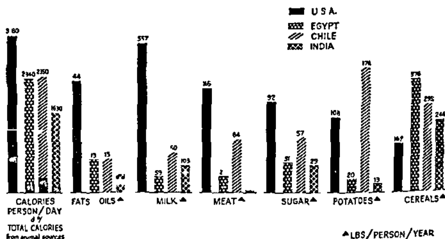


FIG 2 Stamler J (22 23) (for source of data *cf* ref (41) Fats and oils are the amounts of these foodstuffs available for consumption as such not the total amount of fat derived from all dietary constituents

Hence, longstanding gross undernutrition has ceased to be a significant mass phenomenon in the economically developed countries Most people ingest a diet providing them with enough calories except under conditions of war or depression In fact the caloric intake is frequently in excess of the total required to balance energy expenditure with consequent widespread obesity Moreover, these calories are frequently supplied by a diet of inadequate composition a diet unbalanced in terms of the proportions among foodstuffs The nature of the aberration is (1) an excess of total calories empty calories total fat saturated fat cholesterol refined sugar salt and (2) an inadequacy (relative and/or absolute) of essential nutrients (vitamins minerals essential amino acids and essential fatty acids) and bulk Thus malnutrition of a different type is actually widespread in the economically developed countries—malnutrition in the literal meaning of the word, *bad* nutrition

Hence, the provision of a *well balanced optimal diet*—along lines demonstrated by recent broad advances in nutritional science—is the final goal, as yet unfulfilled for large sections of the population (66)

Chapter 3

Nutrition and Atherosclerosis (*Continued*)

D The Epidemiologic Findings

1 *Economically Underdeveloped Countries vs the United States—Habitual Diet and Atherogenesis* —Conditions of life in general—and patterns of diet and disease in particular—differ markedly in the economically underdeveloped countries and the United States (Fig 2) (40–63, 65–68) Most people in the underdeveloped countries usually consume a diet significantly lower than ours in total calories total protein and animal protein, total fat and saturated fat Unlike ourselves, they rely overwhelmingly upon grains and potatoes—relatively inexpensive high caloric high bulk foods—for their subsistence Hence, their fare is also low in cholesterol

The dietary differences between the economically underdeveloped countries and the United States are multiple and complex Moreover, there are many other areas of differences—racial, ethnic climatic geographic socioeconomic cultural public health and medical It is essential to be concerned with all these variables and their possible bearing upon observed patterns of disease

Clinical pathologic surveys on prevalence of atherosclerosis in the peoples of the economically less developed countries are extensive and consistent (69 70) Clinical atherosclerotic disease (particularly coronary heart disease) and severe morphologic atherosclerosis with myocardial infarction at postmortem examination are rarities at all ages

The focus on coronary disease has a twofold basis First the most extensive data are available on this entity Second this clinical disease is a resultant of the pathologic process of atherosclerosis in a very high percentage (over 90%) of cases (290–292 294 299) Therefore, the prevalence and incidence rates of coronary heart disease apparently are a close reflection of the occurrence of severe coronary atherosclerosis in a given population *This correlation does not necessarily hold to a high degree* for disease at other sites With clinical cerebrovascular disease for example it is difficult to distinguish among cerebral embolism, cerebral hemorrhage and cerebral thrombosis These are processes having different etio-pathologic bases Thus recent pathologic studies indicate that cerebral hemorrhage in hypertensives may be a complication—not

chiefly of atherosclerosis (as has been widely assumed)—but rather of a hypertensive miliary aneurysmal lesion in the smaller cerebral vessels Unlike with coronary disease therefore, it is probably not correct to assume that prevalence and incidence rates for cerebrovascular disease reflect the occurrence of severe cerebral atherosclerosis in a given population (21) This invalid assumption has tended to confuse analysi of international epidemiologic trends (139) For valid comparisons cerebral thrombosis (usually atherosclerotic in its pathologic basis) would have to be separated out from the heterogeneous cerebrovascular disease grouping

As long ago as 1934, the relative freedom from atherogenesis was clearly correlated with life span dietary patterns The following generalization was formulated based on an analysis of 28 papers in the literature (69) "In no race for which a high cholesterol intake (in the form of eggs, butter and milk) and fat intake are recorded is atherosclerosis absent Where a high protein diet is consumed which naturally contains small quantities of cholesterol, but where the neutral fat intake is low, atherosclerosis is not prevalent "

This deduction was based on an analysis of reported clinical and pathological surveys made in China East Africa Egypt, India and Malaya, compared with studies in Austria Germany, the United States, and elsewhere

2 *Economically Underdeveloped Countries—Social Class Differences in Diet and Atherogenesis* —This study yielded another highly relevant finding Data from Egypt and India indicated that within these economically less developed countries significant social class differences were demonstrable in prevalence of atherosclerosis Thus in both the e countries atherosclero is was apparently rare in the poorer classes subsisting largely on cereals whereas it was relatively frequent in the more well to-do classes enjoying a diet high in saturated fat and cholesterol (69) These and other findings indicated that racial ethnic and climatic influences could not be primarily responsible for the observed differences in atherogenesis

During the last two decades surveys in Ceylon Costa Rica East Africa Guatemala India Indonesia Iraq Israel Malaya Mexico, Nigeria Okinawa South Africa Uganda all reinforce the same basic conclusion Significant atherosclerosis is rare in peoples who e diet over the life span is predominantly vegetarian and low in calories total lipids saturated lipids and cholesterol (1 4 5 12 13 21 23 68–102) It is rare clinically and morphologically in both males and females—in marked contrast to the United States where among middle aged males particularly atherosclerotic coronary heart disease is epidemic and a high percentage manifests severe gross lesions in the coronary arteries (2 23 290–292 294 300)

3 *Economically Underdeveloped Countries vs the United States—Cor*

relations among Diet, Serum Cholesterol Lipids Lipoproteins and Atherogenesis —Recent studies have also demonstrated that the correlation may be extended from a twofold to a threefold one—among diet, plasma cholesterol lipid lipoprotein levels and atherogenesis Thus the significantly lower prevalence and incidence of atherosclerotic disease in economically less developed countries correlate also with differences (apparently diet induced) in levels of plasma cholesterol lipids lipoproteins (Figs 3 to 5) (1 4–6, 12–14 22, 23, 67, 71, 72 77 81, 91–99, 103–109)

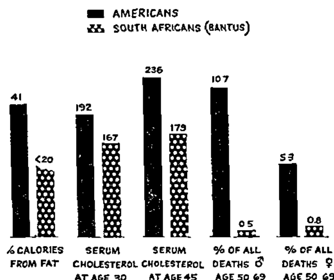


FIG 3 Walker A R P and Arvidsson U B (92) Higginson J and Pepler W J (93) Note the differences in fat intake serum cholesterol level and percent of all autopsied deaths attributed to coronary heart disease Note also the marked tendency for the serum cholesterol of Americans to rise from age 30 to age 45—a tendency virtually absent in the South African Bantu Note also the sex differential in the occurrence of coronary disease in the Americans and its absence in the Bantus (*cf* text and ref 23)

Groups of clinically normal people in these economically less developed nations ingesting a predominantly vegetarian diet low in calories lipids-cholesterol * have mean plasma cholesterol lipid lipoprotein levels signi

*Throughout this book this characterization—diet low or high in calories-lipids-cholesterol is used as a convenient abbreviation for the longer term total calories empty calories total fats saturated fats cholesterol

chiefly of atherosclerosis (as has been widely assumed)—but rather of a hypertensive miliary aneurysmal lesion in the smaller cerebral vessels Unlike with coronary disease, therefore it is probably not correct to assume that prevalence and incidence rates for cerebrovascular disease reflect the occurrence of severe cerebral atherosclerosis in a given population (21) This invalid assumption has tended to confuse analysis of international epidemiologic trends (139) For valid comparisons, cerebral thrombosis (usually atherosclerotic in its pathologic basis) would have to be separated out from the heterogeneous cerebrovascular disease grouping

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3 *Economically Underdeveloped Countries vs the United States—Cor*

factors (1, 5 22, 23 71, 72, 91–100, 103–109, 111–115) (Guatemala data are lacking on upper class patterns of disease)

These findings cast serious doubt upon the validity of the standards commonly accepted in the United States for normal plasma cholesterol concentration They pose the questions Is the life span pattern of diet inducing a chronic low grade hypercholesterolemia in millions of Americans, leading to widespread atherogenesis? What is an optimal serum cholesterol level for optimal freedom from atherosclerotic disease over an optimal life span?

Diet Serum Cholesterol and Atherosclerosis in Middle Aged Guatemalans and North American Males

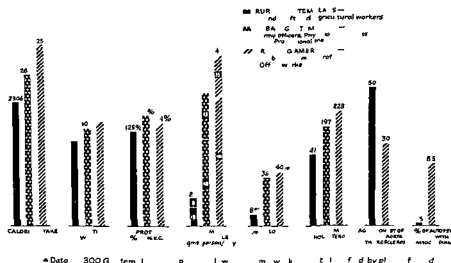


FIG 5 Data from Scrimshaw N S Trulson M Tejada C Hegsted D M and Stare F J (108) Mann G V Munoz J A and Scrimshaw N S (109) Tejada C and Gore I (100) Caloric intake is calories per person per day Relative weight is an index it is the ratio (× 100) of an individual s observed weight to the median weight for his sex height group Protein intake is expressed in relation to the level of daily intake recommended by the U S National Research Council In the fat intake columns the upper values are for vegetable fat the lower for animal fat

Two approaches are identifiable to standard of normalcy The first—and usual—involves measurement of a given index e g serum cholesterol concentration, in an adequate sample of individuals who at the given moment are apparently normal clinically The values obtained are then accepted as indicative of the mean and range of normal A second— and in our opinion more valid—approach involves consideration not only of the momentary but also of the long term medical significance of a given value In arriving at values for normal cholesterol, for example it asks the question What values (mean and range) are consonant with optimal

ficantly lower than groups of clinically normal persons in the United States Moreover, they exhibit a different pattern of change in plasma cholesterol level with age Thus, in middle class Americans plasma cholesterol levels tend to rise with each decade of adult life This pattern is absent in the South African Bantu, but present in the economically more priviledged South African Europeans, whose diet (like that of the Americans) is "rich" in calories-lipids cholesterol (Figs 3 and 4) It is absent in manual laborers in Guatemala and India (largely vegetarians), but present in better off physicians business men, officials, army officers ingesting a high calorie, high fat high saturated fat diet (Fig 5) The several population groups in India generally exhibit corresponding dif ferences in incidence of coronary heart disease—again pointing to the inconsequential role of ethnic and climatic, in contrast to nutritional

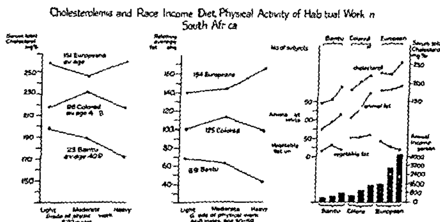


FIG 4 Brock J F and Bronte Stewart B (96) Keys A Anderson J T Aresu M Biörck G Brock J F Bronte Stewart B Fidanza F Keys M H Malmros H Poppi A Postelli T Swahn B and del Vecchio A (159) Relative average fat intake (2nd graph) is the ratio (X 100) of the fat intake of the given group to the mean fat intake for all 9 groups Data on fat intake were obtained by semiquantitative weekly dietary surveys which assumed that each individual consumed an average helping By this method fat intakes were apparently estimated in grams per person per day and apparently converted into fat units (3rd graph) by dividing by 3 15 It was estimated *that the Bantu consumed 17 per cent of total calories in the form of fats the Coloured* 25 per cent and the Europeans 35 per cent The greater total fat intakes with greater incomes were due to greater intakes of animal (chiefly saturated) fat not vegetable fat Note the correlation between cholesterolemia and race income total fat intake animal fat intake Note that for any gi en ethnic group cholesterolemia correlates with income total fat intake animal fat intake—i e race *per se* is apparently not a decisive influence Note the lack of correlation between cholesterolemia and grade of physical work.

The Bantu group is a predominantly Negro group modified historically by Hamitic (Southern Arabian) influence The Bantu migrated from central equatorial to southern Africa. The term Bantu is mainly linguistic in s gnificance The Cape Coloured group is a mixture of the original Hottentot inhabitants of southern Africa Indonesians Malayans and whites The European group is made up of whites of European stock born and reared in the Union of South Africa (96)

Serum Cholesterol in several countries and percent of calories from fat

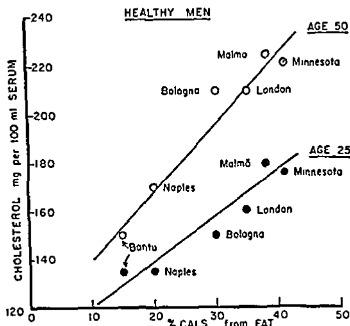


FIG 7 Keys A (122)

Diet & Cholesterolemia in 284 Clinically Healthy Japanese Men Age 40-49 in seven groups

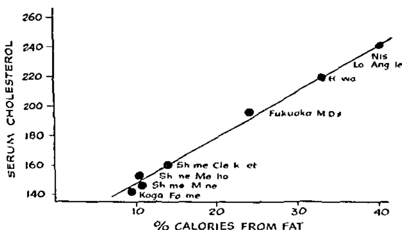


FIG 8 Keys A (107) Note the similar low levels of serum cholesterol in Japanese farmers miners mechanics clerks—values correlating with habitual diets low in fats and not with occupation and physical activity of work Note the higher serum cholesterol concentrations in Japanese physicians and in Japanese Hawaiians and Japanese Americans—again correlating with dietary patterns

freedom from atherosclerotic disease over an optimal life span? Newer research knowledge has brought us to the point where it seems essential to re define standards of normalcy for serum cholesterol, based on this latter approach

4 *Italy and Japan vs the United States* —Significant findings concerning the relationship between diet and atherosclerosis have been forth coming recently also from countries intermediate in the scale of economic development, *e g*, Italy and Japan Thus, vital statistics data reveal that these countries manifest markedly lower heart disease mortality rates than our own, due principally to the relative rarity of coronary heart

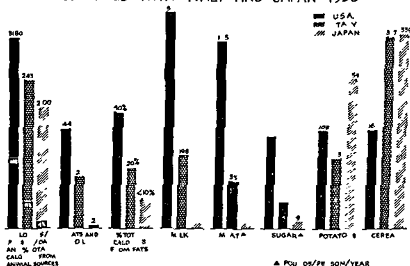


FIG 6 Stamler J (22 23) (for sources of data *cf* refs 41 and 42)

disease At the same time the people of Italy and Japan *en masse* consume a diet much lower than our own in total calories empty calories total fats, saturated fats and cholesterol (Fig 6) (5, 6 22 23, 40–42 61 62, 65 68, 71 72, 81, 91 99 105–107 116–121 123)

Further recent studies of the clinical pathologic survey type indicate that the threefold correlation—among diet plasma cholesterol lipid lipoprotein levels and atherogenesis—is also demonstrable for large sectors of the populations of Japan and Italy (and Spain as well) (Figs 7 to 9) (5, 6, 22 23 71 72 91 99 105–107 118–121 123 124) Here again plasma cholesterol levels fail to increase grossly with age Moreover as in South Africa Guatemala Egypt and India more well to do Italians Japanese, Spaniards—consuming diets different from those of their poorer fellow citizens but similar to our own—have patterns of plasma lipids,

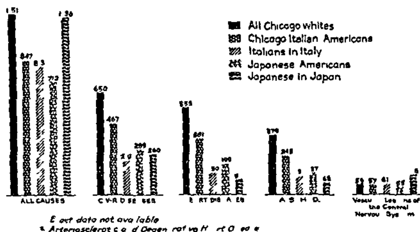


FIG 10 Stamler J (22 23) Stamler J Kjelsberg M Hall Y and Scotch N (126) Note that the Italian Americans have higher death rates than the Italians in Italy The difference is conspicuous for cardiovascular renal diseases heart diseases arteriosclerotic heart diseases The same phenomenon obtains for the Japanese Americans compared with the Japanese in Japan Note also that for these three cause-of death categories the Italian Americans and the Japanese Americans have lower mortality rates than all Americans Finally note the different epidemiologic patterns for mortality due to vascular lesions of the central nervous system—patterns probably reflecting chiefly hypertensive (not atherosclerotic) vascular disease in this age group (21 23 196 230)

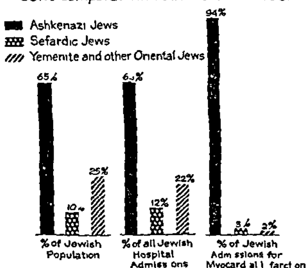


FIG 11 Dreyfuss F (132) Dreyfuss F Toor M Agmon J and Zlotnick A (128) Note that the Yemenite Jews constituted 25 per cent of the Jewish population of Israel and 22 per cent of all Jewish hospital admissions but only about 2 per cent of all Jewish admissions for myocardial infarction Contrast this with the Ashkenazi (Eastern and Central European) Jews (Sefardic Jews are of Spanish origin)

and morbidity and mortality due to coronary heart disease, approaching those prevailing in the United States

These findings again emphasize that ethnic and racial factors are not primarily responsible for the international epidemiologic pattern of coronary heart disease Moreover, they decisively reinforce the general thesis that life span pattern of diet is a critical factor in the causation of the variable incidence of atherosclerosis among different peoples

Incidence of high grade Coronary Sclerosis in consecutive autopsies US vs Japan

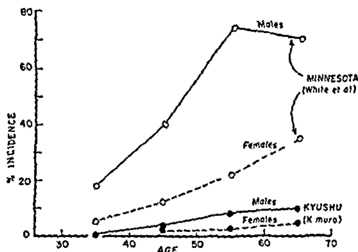


Fig 9 Kimura N (116) White N K Edwards J E and Dry T J (293) Note the markedly higher incidence of severe coronary sclerosis in American males at all ages Note also the presence of a gross sex difference for Americans and its virtual absence for the Japanese (cf Fig 3)

5 *Effects of Emigration—Yemenite Jews, Italians and Japanese* —This conclusion is fortified by recent work showing that changes in the mode of life particularly the diet consequent upon emigration are associated with increases in plasma cholesterol lipid lipoprotein levels and in coronary heart disease incidence rates *This has been indicated in studies on Yemenite Jews in Israel* on Italians in the United States and on Japanese residing for many years in Hawaii or the United States (Figs 10 and 11) (*6, 22 23, 71, 72, 81, 99, 107, 125–138*)

6 *The Low Countries the Scandinavian Countries* et al, *and the United States* —Significant data are also available on European populations usually ingesting diets higher than most Italians in total calories total

fluence of relatively high intakes of unsaturated marine oils on cholesterolemia and atherogenesis in the populations of these countries (167)

A negative correlation was noted between intake of vegetable lipid and death rates attributed to arteriosclerotic heart disease (or arteriosclerotic plus degenerative heart disease) This finding is particularly intriguing in view of recent data demonstrating low serum cholesterol levels in American vegetarians and in Yugoslavs subsisting on diets high in vegetable oils (67, 251) It is also of interest in connection with observations on the reduction of cholesterolemia by incorporation of unsaturated vegetable oils in American type diets

The cited study also noted a positive correlation between protein intake and arteriosclerotic heart disease death rates (139) The question therefore becomes Does the statistical correlation between death rates and levels of total protein animal protein consumption reflect a *cause-and effect* relationship between protein intake and atherosclerotic disease? These data pose this question but cannot answer it The answer must be sought from other available evidence

Extensive experimental data indicate that this is *not* the case (1 451) On the contrary they suggest that high protein intake may afford a partial protection against the hypercholesterolemic and atherogenic effects of high fat high cholesterol diets (454 455 458 482 504–516) On the other hand, extensive clinico-pathologic and animal-experimental data indicate that the correlation between death rates and intakes of total calories, total fats saturated (animal) fats is significant cause and-effect wise

A considerable spread was noted in the data on diet and death rates as analyzed in this study (139) For several economically developed countries with total fat intakes in the range 30 to 40 per cent of total calories age specific death rates varied from 500 to 600 or more per 100 000 population (*e g* Austria West Germany, Sweden Norway Denmark the Netherlands Australia Canada Finland) A few of these countries manifested middle aged death rates considerably lower than those for the United States (739 per 100 000)

Based on findings of this nature several recent reports critically reviewed the problem of the relationship between intake of lipids (total and saturated) and occurrence of atherosclerotic coronary disease (139–143) These critiques have in turn been recently subjected to penetrating analysis (101) In evaluating these critiques it is appropriate to note that the broad statistical data—despite their recognized limitations—*verified* significant overall correlations between death rates and intakes of total calories total fats and saturated fats (Fig 12) (139) These findings therefore did *not* refute the validity of the correlation A valid conclusion—considering the scatter in the data (as well as other evidence)—is that the correlation among diet serum cholesterol and coronary disease is not reflective of a one to-one cause and effect relationship

fats, saturated fats and cholesterol (Figs 7 and 12) (1, 5, 6, 22, 23, 25, 40–42, 65, 67–72, 90, 91, 97, 107, 139–160) Thus, serum cholesterol levels were found to be consistently higher in Swedish population groups compared with Italians (Fig 7) The former had values almost as high as those typically recorded in the United States Serum cholesterol levels in middle aged males (firemen and Rotarians) in Helsinki, Finland were 260 mg %, exceeding those for the United States (107) By 1950, the

Rank correlation coefficients (r) between various dietary components and death rates for 22 countries --Males age 55-59

Dietary Component	Arteriosclerotic and Degenerative Heart Disease	Arteriosclerotic and Degenerative Heart Disease and other Diseases of the Heart
total calories	0723	0593
calories from fat	0659	0470
calories from animal fat	0684	0562
calories from vegetable fat*	-0236	0282
calories from protein	0709	0694
calories from animal protein	0756	0695
calories from vegetable protein	-0430	-0153
calories from carbohydrate	0305	0423
% calories from fat	0587	0390
% calories from animal fat	0677	0557
% calories from vegetable fat*	-0468	0509
% calories from protein	0172	0465
% calories from animal protein	0643	0608
% calories from vegetable protein	-0651	0483
% calories from carbohydrate	-0562	-0386

*Number of countries (N) 21 (data not available for France) otherwise N = 22

Critical Values of r		
N	α = 005	α = 002
21	±0438	±0521
22	±0428	±0508

Fig 12 Yerushalmy J and Hilleboe H E (139)

effects of World War II had receded and prevalence and incidence of atherosclerotic coronary heart disease were again sizable in the Scandinavian and Low Countries (1 5 68 72 107 139–142 157–166)

Calculation of rank coefficients of correlation for 1950 data for 22 countries demonstrated statistically significant correlations between death rates and intakes of total calories total fats and animal fats (Fig 12) (139) One of the problems needing further investigation is the in

In any attempt to arrive at a tentative judgment in this matter, the following facts stand out Cardiovascular renal death rates for middle-aged white males have been high throughout the last 30 to 40 years However the rate did not stay constant during this period in males but rose noticeably In contrast, middle aged white female rates declined markedly (Fig 13) (184) Problems inherent in the available statistics render difficult any evaluation of the trend of death rates over the last 30 to 40 years for arteriosclerotic heart disease *per se* Hence, an inter

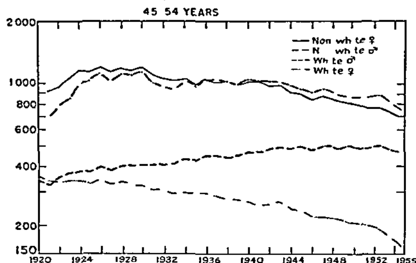


FIG 13 Moriyama I Woolsey T and Stamler J (184) The trends for middle aged whites are discussed in the text Note that Negro rates are higher than white throughout the 35 year period due principally to the several fold higher mortality rates from hypertensive and related diseases in Negroes Note also that the sex differential in mortality rates for Negroes is slight compared with whites due chiefly to the high death rates in Negro females (*cf* Fig 1) This pattern is different than in the economically less developed countries where the low order of the sex differential is due chiefly to low male death rates (*cf* Figs 3 and 9)

pretation must be made of the data for a broad grouping of several diseases the cardiovascular renal diseases (172 173 180 183 184 195) The question therefore arises if the rise in white male rates is chiefly an apparent one due merely to changes over the years in diagnostic acumen and death certification procedures (as some investigators have suggested) —why then have these changes produced a rising trend only for males?

As is well known atherosclerotic coronary heart disease is common in middle aged American male whereas it is remarkably rare in premenopausal females (Fig 1) (1–5 12–23 71 90 134–137 143 155, 172–187,

Further, a number of the countries—particularly the Scandinavian and Low Countries—were in 1950 only a few years away from the privations of World War II, with its significant restrictions in diet and concomitant declines in arteriosclerotic heart disease death rates (1, 5, 6, 23, 71, 72, 101, 143–146, 155, 160–165, 168, 169) It is highly possible that these effects of World War II still found expression in 1950

Moreover, the observed patterns of mortality for these European countries and the United States ranged *in toto* on the *high* side of a distribution curve for middle aged population groups—particularly in comparison with the economically underdeveloped countries Irrespective of the observed differences in rates therefore, coronary heart disease is unquestionably a major public health problem in these European countries, in contrast to the underdeveloped nations

Finally these differences indicate the need for further detailed field studies of the hospital clinical pathological survey type on diet, serum cholesterol and coronary disease The several such investigations accomplished in recent years have in fact yielded impressive data supporting the nutritional metabolic cholesterol lipid lipoprotein theory of atherogenesis (5 6, 71, 107 157–159)

7 *World Wars I and II* —This theory is also amply supported by the findings on time trends of diet and disease in the Scandinavian and Low Countries during World War II This subject was reviewed previously (1), and is therefore not presented *in extenso* here The marked reduction in intake of total calories, total fats saturated fats and cholesterol imposed by the German occupation was associated with a gross decline in arteriosclerotic heart disease mortality rates (1 5 6 23 71, 72, 143–146 155, 160–165) In view of recent clinical research findings on dietary lipids and blood coagulability, it is noteworthy that the occurrence of thrombo embolic episodes also declined in Scandinavia during the war years Hence it has been suggested that the decrease in coronary heart disease rate reflected a diet induced decline in both atherogenesis and thrombogenesis (161) Similar findings were reported from Leningrad during the World War II siege and from Central Europe during the famine years following World War I (10 168 170)

8 *The United States—1910 to 1955* -This whole problem of the trend of atherosclerotic disease over the years—and its relationship, if any to evolving dietary patterns—has recently received the attention of several investigators American and British data suggest a marked increase in middle age mortality rates in these two countries in recent decades (Fig 13) (5 22 23 143–146 155 171–190) The evaluation of these trends however is complicated by a host of statistical and methodological problems—some of them permanently beyond precise quantification because of the nature of the data (23 139, 140 142–146 172–174, 191–194) Hence it is not surprising that disagreements arise concerning the actual degree and extent of the apparent increases in coronary disease mortality (23, 139 140, 142–146 172–174, 178, 180, 183 184 195)

and has remained so—much higher even than in most other economically developed countries (Fig 14) (210–212) Another unique American dietary characteristic—the large intake of butter, lard and other predominantly saturated fats—has apparently been further accentuated, partly as a result of the introduction in 1910 of the catalytic hydrogenation process for converting vegetable oils into plastic shortenings and margarines As a consequence of the hydrogenation process, which saturates double bonds, these fats have a high percentage of *trans* fatty acid isomers

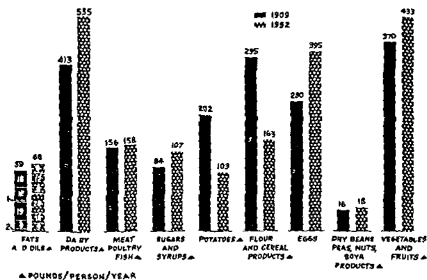


FIG 14 Stamler J (22 23) (for source of the data *cf* ref 212) Data indicate foods available for consumption not foods actually consumed Unlike Figs 2 and 6 based on United Nations sources the data on fats and oils from the U S Department of Agriculture include bacon and salt pork hence the higher values The data on fats and oils are subdivided into specific components from above down they are butter lard margarine bacon and salt side shortening other edible oils Values for eggs are number of eggs per person per year

(23 to 42 per cent) and a low content of essential fatty acids (2 to 8 per cent) (217, 218) Unless enriched they are practically devoid of other essential nutrients *e g* fat soluble vitamins, hence they are an 'excellent' source of empty calories

Intakes of milk dairy products eggs have also exhibited significant increases A marked rise in ingestion of refined sugars (100 per cent empty calories) is another important long term development in the American diet—from 8 pounds/person/year in 1820 to 30 in 1860, 66 in 1900 and 95 today (210–212) All these upward trends have been as-

196–206, 208, 209, 294, 461, 645, 646) This sex differenential in susceptibility for middle aged whites is in the order of 5–25 to 1

The 1920–1955 trend of middle aged white male *vs* middle aged white female cardiovascular renal deaths in the United States therefore, reflects the following For males, a sizable rise in coronary disease leading to a net increase in cardiovascular renal disease mortality, despite declining death rates for infectious diseases involving the cardiovascular renal system For females, continued low coronary disease rates, and a marked decline in death rates due to puerperal and infectious diseases of the cardiovascular renal system resulting in a gross fall in overall cardiovascular renal death rates This tentative conclusion is borne out by other data Thus, while life expectancy at birth for Americans has risen by about 20 years since 1900 life expectancy at age 50 has increased only 2 2 years In view of the great advances during these decades in the prevention of death in middle age due to pneumonia and other infectious diseases, tuberculosis luetic and rheumatic heart diseases, subacute bacterial endocarditis diseases amenable to surgical treatment, and others, a greater increase in life expectancy at age 50 might have been anticipated Almost certainly this absence of a marked improvement is attributable chiefly to an increasing mortality from coronary heart disease in middle age (167)

If this foregoing analysis be correct the qualitative judgment must be accepted that a true increase has actually occurred in mortality among middle aged white American males due to atherosclerotic coronary heart disease This conclusion is a widely but not unanimously held one (167 171–190 195)

In terms of the basic problem of the relationship among diet, atherosclerosis and atherosclerotic disease it therefore becomes essential to attempt an evaluation of the evolution of dietary patterns in the United States over the last several decades Here it is important to note that people aged 50 dying of coronary disease in 1950 lived their life span over the years 1900–1950 Those aged 50 dying in 1920 lived from 1870–1920 If life span patterns of diet exert a key influence in the etiology of atherosclerosis then any review of dietary patterns must seek out data on conditions prevailing in the third and fourth quarters of the nineteenth century as well as in the twentieth century

Here again serious methodological limitations exist due not only to a relative paucity of data but to the particular scarcity of information concerning diets in different regions of the country and among different racial, ethnic and socioeconomic strata at different times (*cf* refs 210–213 216) A further difficulty stems from the fact that much of the data on dietary patterns in Americans deals with foods available for consumption, rather than foods actually consumed (102 195) With these shortcomings in mind, it is possible to delineate the following broad trends Meat consumption has generally tended to be relatively high in the United States,

the need for a multifactorial analysis of atherosclerotic disease causation Because of these complexities—and the limitations of both the mortality and the nutritional data, plus the insurmountable obstacles to their further delineation—extreme caution is essential in interpreting them However, it is not inappropriate to note that the concepts of the nutritional metabolic cholesterol lipid lipoprotein theory are certainly not contradicted by these data

9 *The United States—Morbidity and Mortality Findings in Different Population Groups and Geographic Areas* —It has come to be widely recognized that this country—with its large population stratified by region occupation, income ethnic and racial background—constitutes an excellent epidemiologic "laboratory " Based on this approach, one of us (J S) initiated a long term investigation on the epidemiology of the major cardiovascular renal diseases in the city of Chicago and the state of Illinois (19 21–23 125 126 196, 197, 228–230)

First an analysis of 1951 and 1953 mortality data was undertaken for specific groups in the population stratified by age sex race, nationality, occupation, place of residence—with a particular focus on the middle decades of life (Figs 1, 13 and 15) The following findings are of particular significance The death rates for arteriosclerotic heart disease were several fold higher in middle aged white men than women (Fig 1)—an observation fully in accord with extensive data from multiple sources (1–5 12–23 71 90, 134–137 143 155 172–187, 196–206 208 209 294 461 645 646) It is quite unlikely that diet is a major factor responsible for this gross sex differential since diets of American males and females are probably not markedly disparate (22 23, 102 231) This is a problem meriting further study in view of the paucity of extant data and evidence suggesting that obesity is more prevalent in white men than women (254) This sex differential in coronary disease morbidity and mortality in a population habitually ingesting a diet high in calories-fats cholesterol is either absent or much less marked in economically less developed countries—chiefly because rates for middle aged males are much lower in the latter countries (*cf* Figs 3 and 9) This finding illustrates the interplay between diet and other factors in the etiology of atherosclerotic disease When the diet is non atherogenic coronary rates are low in both sexes When the diet is atherogenic the susceptible male sex manifests a high rate in middle age The resistant female sex continues to exhibit a relatively low rate (although a rate somewhat higher than her counterparts in the economically less developed countries)

With respect to this problem Negroes in the United States appear to present a unique pattern The sex differential is apparently much less marked than for whites chiefly because Negro female rates are relatively high (Figs 1 and 13) Further work is needed to delineate the parameters and bases for this phenomenon (23 196 228–230)

These complex facts concerning the sex differential again serve to em

sociated with a steady decline in grain consumption, of such marked proportions that for tens of millions of Americans today bread can hardly be designated the "staff of life" (Figs 2, 6 and 14) (210–212) A qualitative metamorphosis in flour has also occurred over the decades, i e, a decline in percentage utilization of whole meal The resultant nutritional losses have been only partially compensated by the limited bread enrichment measures of recent years (224–226) The increased consumption of highly processed, refined foods has also involved a decline in intake of bulk—a decline only partially compensated by the increased ingestion of fruit and vegetables Little work has been done on the possible implications of this trend for health and disease (*cf* refs 92, 93, 227)

Because of the limited data on food actually consumed (as distinct from food available for consumption), and the related difficult problem of estimating waste of fats in cooking, some investigators doubt the validity of data indicating an increase in fat consumption by Americans during the last 40 to 50 years (102, 195) It is noteworthy that these writers are also skeptical about the data indicating an increase in coronary disease incidence in middle aged males over these years (195) Thus, these authors imply that both fat intake and coronary disease incidence have been high since the turn of the century If these are actually the facts, and the two phenomena are so correlated this certainly is not inconsistent with the nutritional metabolic theory

In this connection, one other problem merits attention Even if fat intake has increased since the turn of the century, it was—as already noted—high even then If coronary disease incidence in middle aged males was much lower then, as some data suggest why *this* lack of correlation? This possible disparity serves to re emphasize that the relationship between diet and disease is not one to-one that multiple factors interact with diet to influence occurrence of coronary disease With respect to the trends over the last 40 to 60 years, attention needs to be focussed on the interplay between diet and psychological stress, and particularly between diet and large muscle activity

The slight decline in mean total calorie ingestion between 1910 and 1950 must be assessed in terms of another related phenomenon, the decline in physical activity The problem of the possible effects of sedentary life on lipid metabolism and atherogenesis is discussed below

Viewed overall these trends are—within the limitations noted above—highly suggestive of a definite increase (relative and absolute) in consumption of total fats saturated fats cholesterol refined carbohydrates and empty calories (210–212 219–223)

These apparent changes with time in patterns of diet and disease may or may not be significantly interrelated cause and effect wise Thus these decades witnessed other manifold changes in American life e g increase in urbanization, automobile transportation cigarette consumption, sedentary work, and other similar changes—phenomena emphasizing

tive epidemiologic studies—corroborate the basic finding that coronary heart disease is widely prevalent in middle aged American males of most population subgroups (2, 10 22 25 69, 126 172–188 196, 197 199 206, 208, 209, 232–237, 260–278 290–292 294 300)

Several studies—in different parts of the country over the last two decades or more—have yielded disparate results on the problem of the relative incidence of coronary disease in Negroes and whites (10, 23, 172–

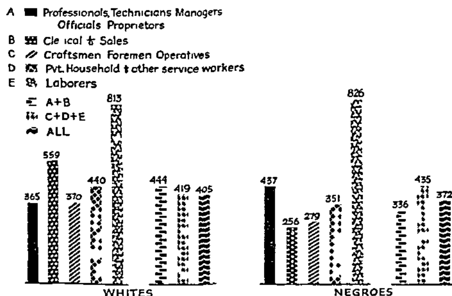


FIG 15 Stamler J (23) Stamler J Kjelsberg M and Hall Y (196) It is likely that the death rates for the laborers are falsely high probably due to inaccurate listings of occupation on death certificates The data were therefore pooled into two broad groups—white collar workers (A + B) and blue collar (manual) workers (C + D + E)

180 196 199 206 208 228–230 260–271 274–277) In contrast it is generally agreed that hypertensive disease is several times more frequent in Negroes than whites (23 196 261)

Data from Norway indicate that a situation similar to the United States prevails for that country (160) The data concerning Great Britain are more complex There a social class difference in arteriosclerotic heart disease mortality has been observed for several decades—a finding complicated by the fact that an opposite social class distribution has been recorded for so-called degenerative heart disease (150–153) Conspicuous in these data is the trend for coronary disease death rate to

phasize that no simple one to one relationship exists between diet and atherosclerotic disease The full significance of this conclusion is discussed subsequently at length

High arteriosclerotic heart disease death rates were recorded for the city of Chicago, for other Illinois municipalities and for rural Illinois (2 , 23, 197) However, a certain differential was noted, i.e., relatively higher rates for Chicago lower for rural Illinois These observations are in accord with data from other states (175, 183, 232 23o) (cf also refs 234-237) Here again, the possibility must be investigated of multiple causative factors operating to produce this apparent result, since dietary patterns in urban and rural areas, at least of the northern United States, are not markedly different (22, 23 107, 197, 210–214, 219–223, 238–253) (Rural southern Negroes may be—or may have been—to a degree exceptional in this regard [238 239]) This fact suggests that the high calorie lipid cholesterol diet of most Americans, urban and rural, (22 23 107 197 210–214 219–223 238–253) as compared to less developed countries, does in fact result in extensive atherosclerotic disease, irrespective of other factors possibly operating to produce differential effects in urban *vs* rural areas

Analysis of the foreign born by nationality leads to a similar conclusion Thus, death rates were high for all nationality groups—considerably higher than those for the given nationalities in their countries of origin (Fig 10) (22, 23 126) (cf refs 6 68 71 72 81 99, 102, 107, 116–121, 123–127, 132–137 139–148 150–160 165) However a moderate range in rates was recorded with the distribution tending to parallel that for the countries of origin The foreign born nationalities therefore *bear the* stamp of their tenure in both their countries of birth and in the United States This is probably true not only for the death rates but also for the dietary patterns of these first generation Americans Their nutritional habits represent an amalgam of old country and American dietetics (22 23, 107 126, 133 135 216) One subgroup of the American Indian ethnic grouping—the Navajo—has recently been the subject of several reports differing in their conclusions (107 256–259) The much discussed, but inadequately studied Eskimo was analyzed in detail previously (1 *cf* also ref 107) Therefore without discounting the possible influence of other factors these findings are consistent with the concept that diet plays a key (although not exclusive) role in the causation of atherosclerotic disease

The analysis of Chicago mortality data also revealed that coronary heart disease death rates were high for middle aged males of both Negro and white races and of all occupation income groups (Fig 15) (19 22 23 125 196 228–230) (*cf* refs 10 69 172–180 183–188 199 206 208 209 232 233 260–273) The toll from atherosclerotic disease was at least as great in the poorer strata as in the more well to do Considerable data *from other sources—e g* life insurance statistics and findings of prospec

lower economic groups in the United States have—at least since the end of the depression in 1939–40—been consuming sizable amounts of meat, milk, eggs, fats and oils, white flour products, refined sugar, salt Their intakes of total calories and empty calories saturated fats (animal and vegetable), cholesterol tend to be virtually as high as those of upper income Americans (Fig 16) (22 23, 107, 196 197, 210–214 216, 219–223, 238–253) (As already indicated, rural Southern Negroes may

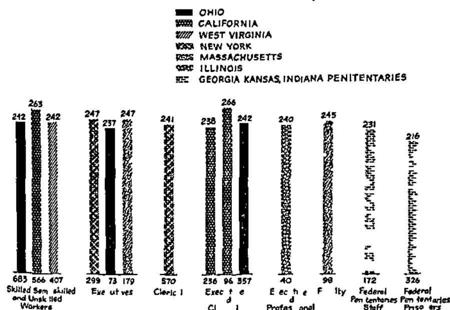


FIG 17 Lewis L A Olmsted F Page I H Lawry E Y Mann G V Stare F J Hanig M Lauffer M A Gordon T and Moore F E (111) The subjects are almost exclusively white Note the similar high mean serum cholesterol levels in different groups of middle aged American males irrespective of occupation and geographic region The single exception is the group of Federal penitentiary prisoners with a somewhat lower mean value Dietary data on this group would be of considerable interest The particularly high values for Californians also remain to be accounted for

be—or may have been—exceptional in this regard [23, 238 239]) Thus most social strata in our country ingest an habitual diet that is potentially atherogenic Therefore the finding that coronary heart disease is prevalent among most sections of the American population does not contradict, but rather lends additional strong support to the theory of a decisive interrelationship between life span pattern of diet and atherogenesis

rise over the recent decades while the social class differential narrowed (144–155) It would seem that Great Britain may be experiencing an increase in the incidence of this disease, embracing all sectors of its population Despite this increase, death rates in Great Britain were in 1950–1954 still considerably below those for age sex race matched groups in the United States Nonetheless, in Great Britain—as in Norway and the United States—this disease has apparently become widespread in the middle aged male population of all social classes

FOOD CONSUMPTION OF LOW AND HIGH INCOME URBAN FAMILIES
U S A -1948

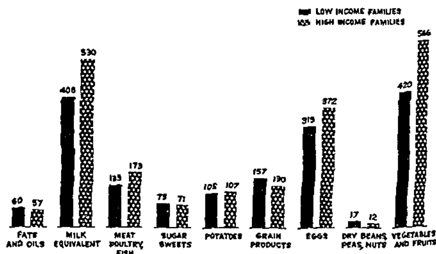


FIG 16 Stamler J (22 23) (for source of data *cf* ref 213 see also ref 214) (*cf* legend Fig 14) These data represent foods available for consumption not foods actually consumed Data for 1955 reveal essentially similar findings among different income groups in various sections of the country (214)

These findings forcefully pose an important question Why is it that the poor in countries like Egypt, Guatemala Japan India, Italy Spain have low coronary disease death rates whereas Americans on the lower rungs of the United States economic ladder have rates at least as high as more well to-do groups? Are these apparently contradictory trends inconsistent with the basic thesis of a key relationship between diet and atherosclerosis? Our present answer is By no means—and for good reasons of fact, namely the important differences that prevail in the dietary patterns of lower income Americans and the poorer classes of all the aforementioned countries (Fig 16 *cf* Figs 2 and 8)

In contrast to the populations *en masse* of these other countries, the

imbalance hypothesis, suggested a few years ago by one of us (J S) (16) for contemporary Americans, particularly lower income Americans, the word malnutrition is applicable in its literal meaning *bad nutrition*

Virtually no evidence has been presented contradicting the thesis that patterns of cholesterolemia in the United States population are a result ant of life span habitual diets Nor have any other hypotheses been ad vanced to account for these patterns of cholesterolemia

11 *The United States—Findings in Prospective Studies on the Living Population* —The basic concepts of the nutritional metabolic theory received further verification in the recently published findings of the Framingham, Albany and Los Angeles epidemiologic studies (2 209, 272, 278) (*cf* also 112, 281) In general, the results of all of these investiga tions point in the same direction When sizable groups of middle aged American males—originally free of clinical coronary heart disease—were followed prospectively the risk of developing this disease was definitely found to be proportional to levels of body weight blood pressure and cholesterolemia (Fig 18) (*cf* foregoing refs to so called retrospective studies dealing with the effects of these variables *cf* also refs 283–285 301–318 351, 431–448) Thus from the Framingham report, in the population at risk normal with respect to all three of these variables the 4 year incidence rate was only 10 per thousand This is one fourth the rate for American middle aged males in general (40/1 000/4 years) In contrast in the population at risk with two or three of these variables abnormally elevated the 4 year incidence rate was 143 per thousand—a more than tenfold increase in risk compared with the Framingham normals These data are not only of great theoretical and research signi ficance they also have profound implications for the practice of medicine (see below)

The Framingham data also serve to re emphasize the important role of hypertensive disease as a factor in the development of clinical coronary disease during middle age particularly in populations with the pre requisite cholesterol lipid lipoprotein metabolic derangements

At the same time it is also essential to recognize that the incidence of coronary disease was by no means insignificant in the nonhypertensive middle aged American males followed in these prospective studies The etiology of coronary disease in normotensive per ons therefore remains a key problem

Similarly with respect to obesity Thus while the overweight group in Framingham had a coronary disease rate approximately twice that of the normal weight group the rate in the latter (28/1 000/4 years) was itself a high one

In this regard available data on obesity and cholesterolemia are worthy of attention In at least two studies a positive correlation has been demonstrated between serum cholesterol levels and body weight but this is a *low order* correlation (112 283) Put somewhat differently,

10 *The United States—Serum Cholesterol Findings in Different Population Groups and Geographical Areas* —This concept is further reinforced by abundant data indicating that serum cholesterol levels tend to be high in all strata of the middle aged United States population compared with values observed in the people of many other countries (Figs 3, 4 5, 7, 8, 17, 18, 19, 20 and 21) (1, 2, 6, 12–14, 22, 25 71, 72, 92–99, 103–109, 111, *112, 118–121, 123, 124, 127, 130, 133–137, 156–159 195, 209, 251, 272,* 278–281 645) Such findings pose anew the problem of valid standards for normal—and optimal—serum cholesterol The evidence—epidemiologic, clinical and animal experimental—indicates that values less than 200 or even 175 mg % may afford optimal freedom from atherosclerosis and atherosclerotic disease and may therefore be designated normal (in the most profound sense of the term) The animal studies show that in virtually all other species analyzed serum cholesterol levels normally are in a range considerably below that observed in healthy people in the United States (1)

From the standpoint of the nutritional metabolic cholesterol lipid lipoprotein theory of atherogenesis these serum cholesterol findings were the anticipated predicted ones They were expected based on the two foregoing observations—i e the finding of diets high in total calories, total fats saturated fats, cholesterol in most strata of the United States population and the finding of high death rates from coronary disease in these strata

What is responsible for the distribution of serum cholesterol levels in the middle aged American male population and particularly the high mean values, compared with those of other peoples? Extensive data support the concept that this is critically a by product of habitual life span dietary patterns

In this connection one other aspect of contemporary nutrition in the United States may be of considerable importance While many lower income Americans consume a diet about as rich as that of their upper income compatriots *in total calories and empty calories total fats* and saturated fats cholesterol a larger percentage of them ingest suboptimal amounts of certain essential nutrients (vitamins minerals essential amino acids and essential fatty acids) (Fig 16) (22 23 107 197 210–216, 219–225 227 238–253 282)

It is therefore misleading one sided inaccurate and oversimplified to speak of Americans as eating ' too well Their diets tend simultaneously to deviate in *two* directions, away from standards for optimal nutrition towards *overnutrition i e* excess of total calories and empty calories total fats and saturated fats refined carbohydrate cholesterol salt and towards *undernutrition i e* inadequacy (relative and/or absolute primary and/or secondary—see below) in essential nutrients and bulk Therefore it is most accurate and scientific to characterize the dietary problem in the United States today as one of dietary imbalance According to this

imbalance hypothesis suggested a few years ago by one of us (J S) (16) for contemporary Americans particularly lower income Americans the word malnutrition is applicable in its literal meaning *bad nutrition*

Virtually no evidence has been presented contradicting the thesis that patterns of cholesterolemia in the United States population are a result ant of life span habitual diets Nor have any other hypotheses been ad vanced to account for these patterns of cholesterolemia

11 *The United States—Findings in Prospective Studies on the Living Population* —The basic concepts of the nutritional metabolic theory received further verification in the recently published findings of the Framingham Albany and Los Angeles epidemiologic studies (2 209, 272 278) (*cf* also 112 281) In general the results of all of these investiga tions point in the same direction When sizable groups of middle aged American males—originally free of clinical coronary heart disease—were followed prospectively the risk of developing this disease was definitely found to be proportional to levels of body weight blood pressure and cholesterolemia (Fig 18) (*cf* foregoing refs to so-called retrospective studies dealing with the effects of these variables *cf* also refs 283–285 301–318 351, 431–448) Thus from the Framingham report in the population at risk normal with respect to all three of these variables the 4 year incidence rate was only 10 per thousand This is one fourth the rate for American middle aged males in general (40/1 000/4 years) In contrast in the population at risk with two or three of these variables abnormally elevated the 4 year incidence rate was 143 per thousand—a more than tenfold increase in risk compared with the Framingham normals These data are not only of great theoretical and research signi ficance they also have profound implications for the practice of medicine (see below)

The Framingham data also serve to re-emphasize the important role of hypertensive disease as a factor in the development of clinical coronary disease during middle age particularly in populations with the pre requisite cholesterol lipid lipoprotein metabolic derangements

At the same time it is also essential to recognize that the incidence of coronary disease was by no means insignificant in the nonhypertensive middle aged American males followed in these prospective studies The etiology of coronary disease in normotensive persons therefore remains a key problem

Similarly with respect to obesity Thus while the overweight group in Framingham had a coronary disease rate approximately twice that of the normal weight group the rate in the latter (28/1 000/4 years) was itself a high one

In this regard available data on obesity and cholesterolemia are worthy of attention In at least two studies a positive correlation has been demonstrated between serum cholesterol levels and body weight but this is a *low order* correlation (112 283) Put somewhat differently

the middle aged American population ingesting its habitual diet tends generally to be at least slightly obese and to have high values for serum cholesterol, with or without concomitant gross obesity When this high fat, high cholesterol diet is ingested in excess, with resultant development of gross obesity, serum cholesterol levels tend to be slightly—but not

EFFECTS OF OBESITY, HYPERCHOLESTEROLEMIA AND HYPERTENSION ON FOUR-YEAR INCIDENCE OF ARTERIOSCLEROTIC HEART DISEASE IN MEN AGED 45-62

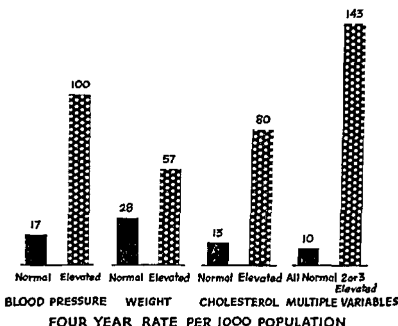


FIG 18 Dawber T R Moore F E and Mann G V (209) Normal blood pressure—consistently below 140/90 elevated blood pressure—consistently 160 or over systolic and/or 95 or over diastolic Normal weight—relative weight under 100 elevated weight—relative weight 113 or over Normal cholesterol—under 225 mg % high cholesterol—260 mg % or above

markedly—higher Given this nutritional metabolic situation it is to be expected that incidence of coronary disease would be substantial in non grossly overweight middle aged American males, and even greater (but not several fold greater) in the obese (Life insurance data indicate that healthy thin persons have a significantly lower risk of coronary disease [284, 285] *No systematic serum lipid data are available on such persons*)

In brief, then, non hypertensive, non overweight middle aged American males—better off though they may be—nonetheless still have a by no means insignificant incidence of elevated serum cholesterol levels and coronary disease The relationship of life-span diet to these phenomena cannot be gainsaid

Chapter 4

Nutrition and Atherosclerosis (*Continued*)

E The Clinical Pathological Findings

EXTENSIVE data from clinical pathological re earch also lend strong support to the dietary metabolic cholesterol lipid lipoprotein theory of atherogenesis

1 *Historical Development* —Before proceeding to recent work it is valuable to review the long term contribution of clinical pathological research in clarifying the interrelationship between diet and atherogenesis For the fact is that historically the initial posing of the problem came primarily as an out growth of pathologic studies In the middle of the last century, cellular pathology identified atherosclerosis as a separate specific lesion among the arterioscleroses—distinguishable particularly by its large content of cholesterol and other lipids Laterally, the intimal foam cell cushion made up of one or more layers of cholesterol lipid laden lipophages, was identified as the earliest histologically recognizable stage of plaque formation in human arteries (1 3)

Data were al o collected indicating that the lipids of the atherosclerotic plaque originated chiefly from the plasma (1 286) Recent findings demonstrating arterial wall synthesis of cholesterol and phospholipids do not constitute a refutation of the conclusion that the accumulated lipids in atherosclerotic plaques are derived primarily and chiefly from the plasma (287–289)

A few workers, particularly in Great Britain adhere to an alternative concept concerning the basic pathogenesis of the atherosclerotic plaque—the thrombogenic theory (449 450)

All these observations by pathology brought to the fore—but could not answer—the critical question Is there any etiologically significant *interrelationship among cholesterol and fat in the diet the plasma and the lesion* (*cf* refs 1 3 4 10 11 69 70 170)? In as essing this contribution of pathology it is worth emphasizing that the proper formulation of a scientific question is often the greatest impetus to its solution

2 *Morphologic Atherosclerosis in Cases with and without Clinical Coronary Heart Disease* —More recently careful pathologic investigations in the United States showed that atherosclerosis of the coronary arteries is generally of greater severity in cases of clinical coronary heart dis-

ease compared with cases clinically free of this disease ante mortem (290–292 294–300) This demonstration is of key practical and theoretical importance for research in this field (see below)

3 *Atherosclerosis in Nephrosis Hypothyroidism Diabetes, Essential Familial Xanthomatosis* —Clinical research long ago noted that athero-

SERUM LIPIDS IN MIDDLE-AGED NORMAL MALES AND MALES WITH CORONARY HEART DISEASE

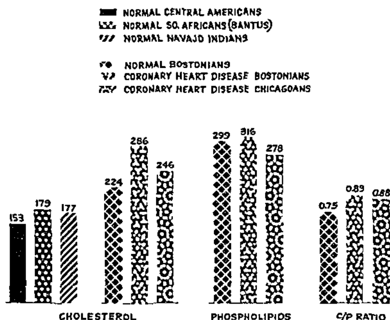


Fig 19 Data on normal Central Americans from Mann G V Munoz J A and Scrimshaw N S (109) on normal South African Bantus from Walker A R P and Arvidsson U B (97) and Higginson J and Pepler W J (93) on normal Navajo Indians from Page I H Lewis L A and Gilbert J (257) on Bostonians with and without clinical coronary heart disease (all men under age 40) from Gertler M M and White P D (202) on Chicagoans with coronary heart disease (all men under age 50) from Stamler J Pick R and Katz L N (645) The data from analyses done in different laboratories are not amenable to strict quantitative comparison

sclerosis was more frequent premature and severe in a number of disease states characterized by a sustained period of hypercholesterolemic hyperlipemia—nephrosis hypothyroidism essential familial xanthomatosis diabetes (1) This observation pointed up the relationship between hypercholesterolemia and atherogenesis in a group of diseases

in which hypercholesterolemia is mainly endogenous (and not diet induced) It therefore lent further support to the concept that atherosclerosis is a metabolic disease However, it did not fundamentally illuminate the problem of the relationship of nutrition to this disease beyond indicating that it was not exclusively diet induced

Serum Cholesterol and Lipoprotein levels in Clinically healthy Americans and in males with Coronary Heart Disease

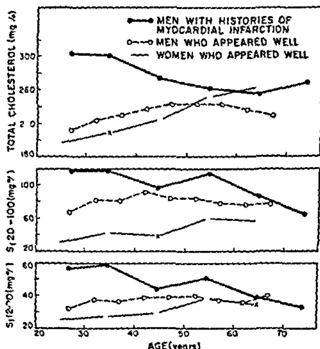


Fig 20 Lawry E Y Mann G V Peterson A Wysocki A F O Connell R and Stare F J (112) Note the differences in serum cholesterol levels between the clinically normal and the myocardial infarction groups Note also that these differences are greatest in the youngest age group and decline with age

4 *Serum Cholesterol Lipid Lipoprotein Levels in Clinical Coronary Heart Disease* — Clinical investigation made a critically important contribution through studies on cholesterol lipid lipoprotein metabolism in patients with coronary heart disease It conclusively demonstrated that any group of middle aged males with coronary heart disease had significantly higher levels of circulating cholesterol lipids β lipoproteins than a

comparable clinically normal group* (Figs 19 to 21) (1, 3–5, 12–14, 21, 22, 69, 71, 112, 171, 202, 279–281, 283 301–318, 645)

It should be emphasized that these observations refer to *group* differences Within any group of middle aged males with coronary heart disease, a small percentage of *individuals* will invariably exhibit low plasma cholesterol levels Correspondingly, epidemiologic and clinical

New Episodes of Coronary Heart Disease in Relation to levels of Serum Cholesterol in the Base Population of Men Age 40-59

Cooperative study on Lipoproteins + Atherosclerosis

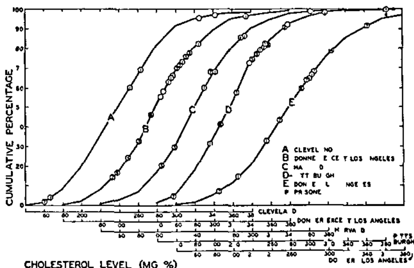


FIG 21 Gofman J W *et al* and Andrus E C *et al* (281) Each circle represents an episode of clinical coronary heart disease in an individual with the indicated value for serum cholesterol prior to illness Note that the 40 per cent of the population with the lower cholesterol levels yielded 23 per cent of the cases (13 of 57) whereas the 40 per cent with the higher cholesterol levels yielded 66 per cent of the cases (38 of 57) (compare Fig 18)

studies demonstrate that a small percentage of cases of clinical coronary disease do in fact develop from people with low normal cholesterol levels (Fig 21) (2 23 72, 93–98 112 116 117 134–137, 209 272 278, 645) It is of decisive theoretical importance that the percentage of such cases is *low* These "exceptions to the rule certainly merit intensive study

*Recent reports have dealt extensively with the comparative merits of serum cholesterol *vs* lipoprotein fractions in segregating coronary patients from clinically normal persons (see particularly refs 112 279 281 and other cited refs) In view of these comprehensive discussions this problem is not dealt with in this review

since elucidation of the etiology and pathogenesis of disease in the e indi v duals should contribute significantly to clarifying the overall problem

It was further observed that the differences in serum cholesterol be tween men with and without clinical coronary disease were greater, the younger the two groups (Fig 20) This difference emerged despite the fact that the "control' group was not really a normal group, but only a *clinically* normal group It was not free of atherosclerosis morpho logically, since most American males by middle age have gross coronary atherosclerosis (290–292 294–298 300) Therefore the two groups rep resented more disease *vs* less-disease, not disease *vs* no-disease

The latter comparison could be made only by analyzing Americans *vs* Bantus or Guatemalans, for example Then the disparity in levels of serum cholesterol lipids β lipoproteins would be even greater (Fig 19)

This comparison—or more precisely contrast—brings once more to the fore several critical questions What are proper standards for normal —and optimal—serum cholesterol? Why do extensive segments of our clinically normal healthy middle aged population have serum cholesterol levels in a range inordinately predisposing them to coronary heart disease? What is the origin of this lipid metabolic derangement? Is life span pat tern of diet a decisive causative factor—and if so what in the diet?

5 *Dietary Effects on Cholesterolemia—Weight Gain and Loss, Low Fat, Low Cholesterol Diets* —The last few years have witnessed a vigorous at tack on these problems by clinical investigation As a result, it has been conclusively demonstrated—contrary to opinions widely held only a decade ago (1, 352)—that serum cholesterol lipid lipoprotein levels of middle aged Americans are highly amenable to alteration by dietary means Thus simple overeating with rapid weight gain was found to be associated with a marked increase in serum cholesterol (283 319–323) Further increased intake of saturated fats (*e g* pemmican) in an iso caloric diet also was correlated with a rise in cholesterol (324 325) These data from human experiments reinforced the conclusion that diets high in calories fats saturated fats cholesterol lead to elevated plasma cholesterol levels

Several clinical studies also indicated that ingestion of a high fat meal is followed postprandially by an increased blood coagulability *in vitro* Clotting time was reported to be decreased irrespective of the type of fat used *i e* animal or vegetable saturated or unsaturated (326–345) It was not altered after low fat meals It should be noted that several negative reports challenge the validity of this observation It has also been reported that ingestion of certain saturated fats particularly butter fat results in a significant retardation of fibrinolysis, *i e*, of the ability of plasma to lyse formed clots No data are available concerning the *in vivo* effects of fat *vs* non fat meals on the clotting mechanism Further more the relationship—if any—of this phenomenon to atherogenesis thrombogenesis, and development of clinical atherosclerotic disease re

mains to be elucidated This is a relatively new area of investigation Undoubtedly it will be thoroughly explored in the next few years At this juncture estimates of the clinical significance of these observations on diet and clotting can at best be only conjectural Should the initial findings receive firm verification, they would constitute a further support for the nutritional metabolic theory, with obvious practical implications for clinical medicine in its efforts to prevent and treat atherosclerotic disease (see below)

EFFECT OF WEIGHT LOSS ON SERUM CHOLESTEROL AND LIPOPROTEIN LEVELS

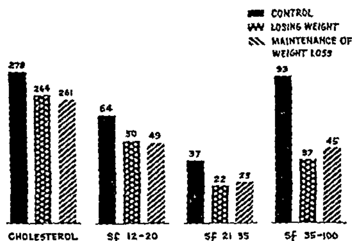


Fig 22 Walker W J Lawry E Y Love D E Mann G V Levine S A and Stare F J (319) cf also refs 320 346 347 Note that during a period of active weight loss serum cholesterol lipoprotein levels fall Note also that they remain at the reduced concentrations with maintenance of weight loss

Clinical investigation also demonstrated that plasma cholesterol concentration may be readily lowered by dietary means It tends to fall during periods of weight reduction (Fig 22) (319 320 346-349) Low fat, low-cholesterol diets also effect such a decline in most patients (Figs 23 and 24) (1, 3-6 12-14 21 22 71 279 319 346-349 351, 353-375) The response apparently occurs irrespective of gross weight loss It tends to supervene rapidly being manifest usually during the initial weeks on diet However on occasion it develops more slowly and gradually The fall in serum cholesterol is often substantial particularly in hypercholesterolemic patients It apparently persists in most persons with continued adherence to the low fat, low cholesterol diet *

*Limited data indicate that addition of cholesterol to this diet without increase in fat intake has little influence on serum cholesterol levels at least in short term experiments (71 107 375 3 6)

6 *Dietary Effects on Cholesterolemia—Unsaturated Vegetable and Marine Oils—Complete Substitution, Partial Substitution and Supplementation Studies* —Varying results were initially obtained in investigations on the effects of substituting unsaturated vegetable lipid for carbohydrates in low fat, low cholesterol regimens Some studies reported a tendency for serum cholesterol to rise again (354, 358 362, 365, 371, 376) Others observed an additional slight reduction in cholesterolemia (Fig 25) (372

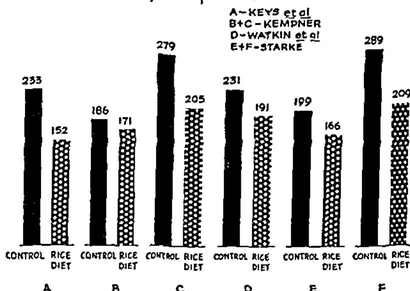


Fig 23 Keys A Mickelsen O Milles E V O and Chapman C B (354) Kempner W (353) Watkin D M Froeb H F Hatch F T and Gutman A B (355) Starke H (350)

377–379) Still others observed essentially no effect (380) The basis for this apparent disparity in results remains to be elucidated It is presumably unrelated to the degree of unsaturation of the vegetable oils utilized (see below) since this was similar in the foregoing studies yielding apparently contradictory data It may be a function of plant sterol or protein content of the respective diets (see below) It is generally agreed that incorporation of saturated animal fat *e g* butter fat led to a re elevation of serum cholesterol however the saturated fat ethyl stearate had no such effect (380)

Several other recent studies investigated the effects of unsaturated oils on cholesterolemia. It was shown that isocaloric substitution of unsaturated vegetable or marine oils for saturated animal lipids in the diet resulted in significant falls in plasma cholesterol levels (Figs. 25 and 26) (166, 365, 369, 370, 372, 373, 375–383, 385–405, 415).

EFFECTS OF REDUCED FAT ON SERUM CHOLESTEROL IN MEN ON DIET CONSTANT IN CALORIES-PROTEIN MINERALS-VITAMINS

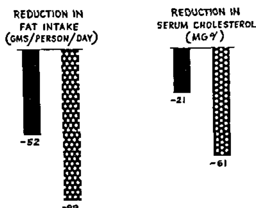


Fig. 24. Keys, A., Anderson, J. T., Fidanza, F., Keys, M. H. and Swahn, B. (364).

The response with substitution of unsaturated vegetable oils for saturated animal fats tended to occur promptly within a few days and persisted for at least several months with continued adherence to this dietary regimen. These experiments were all of the *complete substitution* type, *i.e.*, they uniformly involved the virtually complete exclusion of all animal fats from the diet. In many cases formula diets—with unsaturated vegetable oils supplying as much as 60 per cent of the total calories—were utilized to assure accomplishment of this objective.

Supplementary to this observation is the finding that Americans who are habitual pure vegetarians have significantly lower serum cholesterol levels than omnivores or ovo lacto vegetarians—despite a high intake of total (all vegetable) fat (Fig. 27) (251). This is consistent with previously cited findings in Yugoslavs (67). In this connection the *negative* correlation between vegetable fat intake and arteriosclerotic heart disease death rates for 22 countries is also noteworthy (Fig. 12) (139).

6 *Dietary Effects on Cholesterolemia—Unsaturated Vegetable and Marine Oils—Complete Substitution, Partial Substitution and Supplementation Studies* —Varying results were initially obtained in investigations on the effects of substituting unsaturated vegetable lipid for carbohydrates in low fat, low cholesterol regimens Some studies reported a tendency for serum cholesterol to rise again (354, 358 362, 365, 371, 376) Others observed an additional slight reduction in cholesterolemia (Fig 25) (372

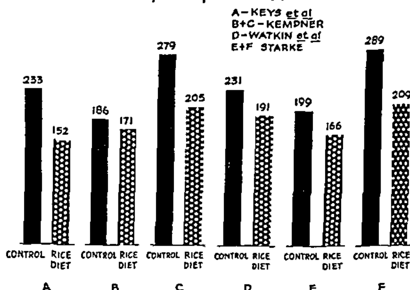


Fig 23 Keys A Mickelsen O Miller E V O and Chapman C B (354) Kempner W (353) Watkin D M Froeb H F Hatch F T and Gutman A B (355) Starke H (350)

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More recently, reports have begun to appear on the effects of only *partial substitution* (Fig 25) (369, 372, 394–398, 406, 407) Thus, in one study a 140 gram fat diet was utilized composed of 40 grams of mixed food fats plus 100 grams of butter—with experimental substitution of 100 grams of unsaturated oil for the butter (394–397) In another study, 100 gram animal fat diets were utilized—with partial substitution experimentally of 70 grams of corn oil for 70 grams of animal fat (leaving 30 grams of animal fat) (398) This partial substitution of unsaturated

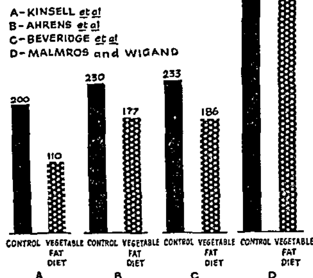


Fig 26 Kinsell L W Partridge J Boling L Margen S and Michaels J (381) (*cf* also *refs 382 383 385–388) Ahrens E H Insull W Blomstrand R Hirsch J* Tsaltas T T and Peterson M L (393) (*cf* also refs 372 and 392) Beveridge J M R Connell W F Mayer G A Firstbrook J B and DeWolfe M S (377) Malmros H and Wigand G (365)

Fig 25 Beveridge J M R Connell W F and Mayer G A (378) Note in the upper figure the decline in serum cholesterol with a fat free diet This decline proceeds further with a diet containing 60 per cent of calories from corn oil It is partially reversed with a diet containing 20 per cent of calories from butter completely reversed with 60 per cent of calories from butter Note in the middle figure the decline in serum cholesterol with complete substitution of a corn oil formula diet This decline is partially reversed in a few days when the corn oil is replaced by butter chickenfat lard or beef Note on the lower figure the decline in serum cholesterol with partial substitution of corn oil for butter fat

Effects of various types of formula diets on Cholesterolemia

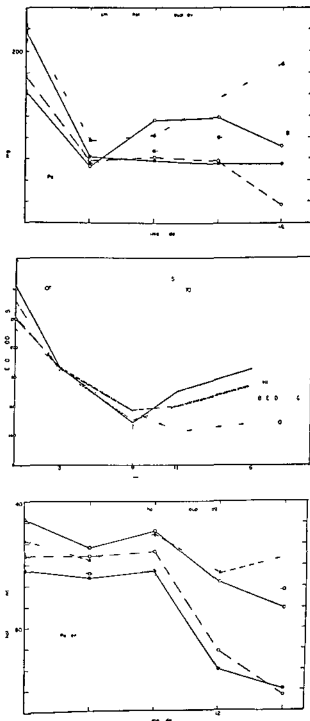


FIG 25—*Legend on opposite page*

Such a supplementation regimen rigidly applied, would tend, of course, to increase total caloric ingestion On this basis alone, a rise in serum cholesterol might have been anticipitated (see above) In actuality subjects in some cases spontaneously adjusted their *ad lib* normal diets, thereby accommodating for the extra calories and avoiding weight gain In such supplementation studies a fall in plasma cholesterol was reported by one laboratory in limited experiments on a few South Africans (Fig 28)

Effects of a Supplement of Essential Fatty Acids on Serum Lipids in a Patient with Hypercholesterolemic Hyperlipemia

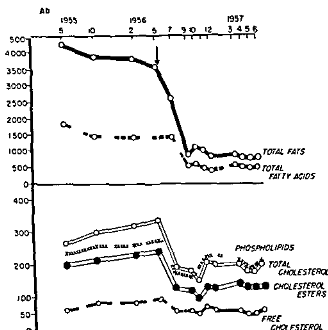


Fig 29 Nothman M M Bellin L and Proger S (410) The arrow (↓) indicates the date of onset of daily supplementation with the mixture of essential fatty acids

(379) This was the case even when one of the animal fat sources (eggs) also yielded a high cholesterol intake On the other hand studies by other groups yielded less clearcut results (Fig 28) (383 385 408 409) Further another group reported that addition of fat—either vegetable or animal—to a mixed diet induced increased cholesterolemia (376–378 389–390) Precise experimental design and specific data from this study were not presented

At the October 1957 meeting of the American Heart Association, im

oils for saturated fats was also effective in lowering serum cholesterol levels

Another variation in experimental design has been explored, *viz* unsaturated vegetable oil *supplementation* of a high calorie, high fat, high saturated fat, high cholesterol diet This involved neither withdrawal of fat, nor any other departure from the customary fare

NUTRITIONAL AND BIOCHEMICAL FINDINGS IN OMNIVOROUS VS HERBIVOROUS AMERICANS

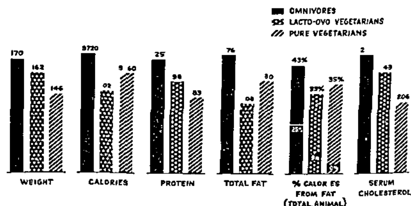


Fig 27 Hardinge M G and Stare F J (251) Note the markedly lower serum cholesterol level in the pure vegetarians on a diet of 130 grams of vegetable fat per day *(35 per cent of calories)*

EFFECTS ON SERUM CHOLESTEROL OF VEGETABLE FAT SUPPLEMENTATION OF AN ANIMAL FAT CONTAINING DIET

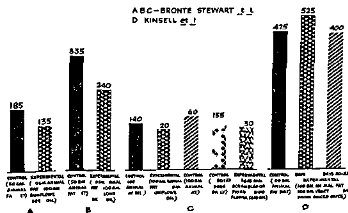


Fig 28 Bronte Stewart B Antonis A Eales L and Brock J F (379) Kinsell L W Michaels G D Cochrane J C Partridge J W Jahn J J and Balch H E (383) Note the tendency for cholesterol levels to fall with vegetable fat supplementation of an animal fat containing diet

volved (382, 383, 385–388, 393, 403) On the other hand, one group of investigators has presented considerable evidence to support their conclusion that plant sterols are decisively responsible for the cholesterolemia reducing effects of such products as corn oil (376–378, 389, 390, 414) Further work is apparently needed to resolve this disagreement

The serum cholesterol response with vegetable and marine oils has also been attributed to their high content of unsaturated fatty acids This

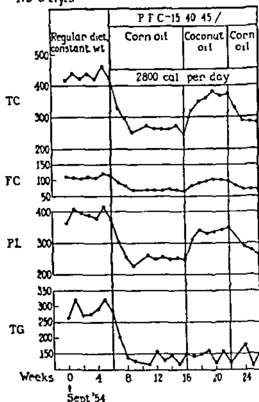


FIG 30 Ahrens E H Insull W Blomstrand R Hirsch J Tsaltas T T and Peterson M L (393) Note the renewed elevation of serum cholesterol and phospholipids with transfer from corn oil to coconut oil (high in saturated fat) formula diet P F C dietary protein fat and carbohydrate as percent of total calories TC and FC total and free cholesterol respectively PL phospholipids TG triglycerides

pressive data were presented demonstrating marked, consistent falls in serum total lipids, fatty acids, cholesterol and cholesterol/phospholipid ratios in 22 hypercholesterolemic patients given 25 to 30 cc daily of a mixture of linoleic acid (49%), linolenic acid (49%) and arachidonic acid (2 per cent) (Fig 29) (410) There were no dietary restrictions The results, therefore, represent the effects of unsaturated oil *supplementation* —in this case unsaturated oils of the polyethenoic, essential fatty acid (EFA) type (see below)

Positive results with safflower oil (300 cc daily) "supplementation" (isocaloric) were also reported to the 1957 meeting of the American Society for the Study of Arteriosclerosis by another investigator in studies on diabetics (411) It was further noted that spontaneous retinal hemorrhages ceased to occur during the period of safflower oil ingestion and that tourniquet tests revealed decreased capillary fragility (411)—a finding apparently confirming a previous report that essential fatty acids enhance capillary integrity (412) This finding is particularly intriguing in relation to the problem of intramural hemorrhage in atherosclerotic plaques as a significant mechanism in the conversion of morphologic coronary lesions into clinical coronary heart disease (413)

7 *Essential Fatty Acids and the Mechanism of the Effects of Unsaturated Oils* —Extensive studies are being reported on the factor or factors responsible for the decline in cholesterolemia in these experiments with unsaturated vegetable oils, and the mechanism of their effect From observations to date it has been suggested that in the substitution experiments removal of dietary cholesterol was not significantly responsible for the observed results Thus, addition of cholesterol to a vegetable oil diet induced little or no renewed rise in serum cholesterol level (372 375–379 382 383 385 389, 390)

In the few such studies reported to date cholesterol was added to a *purified formula ration high in unsaturated vegetable oils and low in* saturated animal fats Under these conditions a slight rise in serum cholesterol supervened over a relatively short time course (1 to 10 weeks) Very different results have been obtained in several experimental animals *i e* the development of severe hypercholesterolemia with the incorporation of cholesterol and unsaturated vegetable oil in the diet (see below) In view of these findings, additional studies are needed before any conclusions are justified concerning the interrelated effects of cholesterol and different fats on cholesterolemia in man It may well turn out that the findings in substitution studies result from removal of dietary fats and cholesterol

In other studies evidence was obtained indicating that the cholesterolemia reducing influence of unsaturated vegetable oils could not be attributed to their content of phospholipids (382 383 385–388) It was also tentatively concluded by some workers—based on their research findings—that the plant sterols in vegetable oils are not critically in

a basal low fat diet of natural foodstuffs (380) Feeding the saturated fat, ethyl stearate with this diet was also associated with a fall in serum cholesterol—a finding possibly related to incomplete absorption of this lipid Two other groups of investigators also observed that feeding a corn or safflower oil formula diet resulted in a marked rise in serum EFA, specifically a more than two-fold increase in the linoleic acid content of serum cholesterol esters and phospholipids and an elevenfold elevation in the amount of this FFA in triglycerides (402, 423)

These observations with pure lipids seem to indicate that neither phospholipids nor plant sterols nor oleic acid are essential factors in the serum cholesterol response with vegetable oils in either substitution experiments with formula diets or supplementation experiments with *ad lib* mixed diets They are consistent with the hypothesis that the essential fatty acids in unsaturated vegetable and marine oils are decisive factors in the mechanism of their effect on serum cholesterol However they do not represent definitive proof of the validity of this hypothesis

Recent reports have also served to clarify the mechanism of action of unsaturated oils on cholesterol metabolism Thus it was shown in tracer studies using cholesterol-4 C^{14} that changing a hypercholesterolemic patient s diet from *ad lib* feeding to a 40 per cent butter formula—with a resultant rise in plasma cholesterol from 478 to 720 mg %—was associated with a marked decrease in fecal sterol excretion When corn oil replaced the butter plasma cholesterol decreased to 350 mg % Concomitantly fecal excretion of cholesterol and its end products rose markedly (424) The data strongly indicated that fecal cholesterol is derived from the plasma and that bile acid excretion is not a major pathway for disposal of cholesterol by the human organism Moreover they pointed to the conclusion that the character of dietary lipids influences cholesterolemia by increasing or decreasing the fecal excretion of cholesterol and its transformation products (424 425)

One further observation of a general theoretical nature may be relevant to this whole problem It seems particularly premature to conclude that the basic lipid metabolic derangement leading to atherogenesis is a resultant of *primary* EFA deficiency in human diets The fact is that usual American diets for example are not low in essential fatty acids—quite the contrary Thus butter, margarine and other hydrogenated vegetable fats contain 2 to 10 per cent EFA Milk and milk products have a significant EFA content Animal fats in general are composed of about 9 per cent essential fatty acids (217 218 420 422 427–429) Most Americans therefore ingest large amounts of EFA every day irrespective of their vegetable and marine oil intakes They actually consume much more EFA than most other peoples—much more than any estimated minimum daily requirement Consistent with this fact is the observation that American and British patients with coronary disease do not exhibit ab

interpretation is supported by observations indicating that the pattern of change in serum cholesterol levels correlated closely—but not completely—with the degree of unsaturation (iodine number) of the vegetable oils (372, 379, 393–397) It was reinforced by data showing that serum cholesterol rose anew when saturated vegetable fats (margarine or coconut oil or hydrogenated peanut fat or hydrogenated corn oil) were substituted for unsaturated vegetable oils (Fig 30) (372, 378, 379, 393–397 402) On the other hand, other workers failed to observe this phenomenon 380, 414), hence this aspect of the mechanism problem must also be regarded as *sub judice* at present The apparent disparities in findings in man compared with other species have further complicated the problem (see below)

The unsaturated vegetable oils contain large amounts of both mono- and poly ethenoic fatty acids Oleic acid typifies the former linoleic acid the latter Linoleic acid is one of the essential fatty acids (EFA) (393 416–420) It is not surprising therefore—in view of the high EFA content of unsaturated vegetable oils—that speculation has been rife on the role of essential fatty acids in the mechanism of the cholesterolemia reducing effect (426 *cf* discussion in refs 6 7, 20–23, 71 142 166, 369–373 376–379 381–383 385–400 421 422 426 461)

The achievement of a definitive experimental resolution of this scientific problem is rendered difficult by the lack of available chemically pure lipid compounds Since most unsaturated vegetable oils contain both oleic and linoleic acids in quantity as well as plant sterols and phospholipids results of feeding experiments with them do not readily yield a clearcut differential answer (393)

Recently reports have begun to appear on the effects of feeding pure preparations Mention has already been made of the impressive reductions in serum cholesterol achieved in 22 patients in a supplementation study utilizing 25 to 30 cc of a mixture of three essential fatty acids (Fig 29) (410) Another group initially reported a marked reduction in serum cholesterol in one patient with ingestion of a formula diet containing a synthetic lipid mixture made up of oleic acid (75 per cent), linoleic acid (2 per cent) palmitic acid (19 per cent) and stearic acid (5 per cent) (415) At the November 1957 meeting of the American Society for the Study of Arteriosclerosis these workers reported their results in experiments with ethyl oleate triolein ethyl linoleate (96 per cent pure) trilinolein, and a phosphatide of animal origin containing approximately 12 5 per cent tetraenoic (presumably arachidonic) acid Each of the latter three poly ethenoic EFA preparations produced a significant sustained *fall in* plasma cholesterol associated with a rise in EFA esterified with cholesterol (405) The two mono ethenoic preparations ethyl oleate and triolein were apparently without effect—a finding in accord with the conclusions of others (393–397) Similar results were obtained by another investigator working with an ethyl linoleate concentrate incorporated in

Chapter 5

Nutrition and Atherosclerosis (*Continued*)

F The Animal-Experimental Findings

THE animal experimental laboratory is the third broad source of data concerning the interrelationship among diet cholesterol lipid lipoprotein metabolism and atherogenesis

1 *Historical Development* —In evaluating the contribution made by this methodology, it is important to appreciate the evolution of research in this field Experimental atherosclerosis has a pre-history and a history The dividing line is roughly the year 1910 Up until then every effort to reproduce atherosclerosis in laboratory animals had met with failure Different types of vascular scleroses had been produced by a variety of means but never atherosclerosis (1 10 11 170 461) In 1908–1912 success was first achieved in producing atherosclerosis by feeding animal tissues to rabbits It was soon demonstrated that lipid constituents (*i e* cholesterol and neutral fats)—and not proteins—were the decisive atherogenic factors in this diet (1 451) Thus hypercholesterolemia and atherosclerosis resulted when cholesterol and fat *per se* were added to the feed

2 *Diet induced Hypercholesterolemia and Atherogenesis in Different Species* —In the last decade hypercholesterolemia and atherosclerosis have been induced in all the major laboratory species herbivorous omnivorous and carnivorous (1 3 4 6 12–14 461) In the chick like the rabbit this was achieved by feeding a diet supplemented with cholesterol and oil In these two susceptible species it was further demonstrated that atherosclerosis could be induced without massive hypercholesterolemia and organ lipidosis (Fig 32) (1 451 452) This was accomplished by feeding small amounts of cholesterol lipid over long periods of time In cockerels minimal hypercholesterolemia developed with diets of mash plus ½ per cent cholesterol and 5 per cent cottonseed oil Gross atherosclerosis of the aorta was demonstrable after 35 weeks on this regimen—a time period representing roughly 20 to 25 per cent of the chick s life span (1 452) This approaches the dietary metabolic and temporal prerequisites for atherogenesis in man

In species more resistant than the chick and the rabbit it proved possible to induce hypercholesterolemia and atherosclerosis by using more complex forms of the same fundamental nutritional metabolic alteration

normal, low levels of polyethenoic essential fatty acids in their sera (Fig 31) (104, 430)

Therefore—even if a metabolic deficiency of EFA were actually present in the American population—it could not be the resultant of a primary dietary lack of EFA *per se* It could only be a *relative* deficiency, *secondary* perhaps to excessive intake of saturated fats, cholesterol, refined carbo hydrates and/or total calories This would be a derivative imbalance, with inadequacy of EFA (if actually present) due to an inordinate need stemming from other dietary aberrations and excesses

Unsaturated Fatty Acids in the blood of patients with Coronary Artery Disease

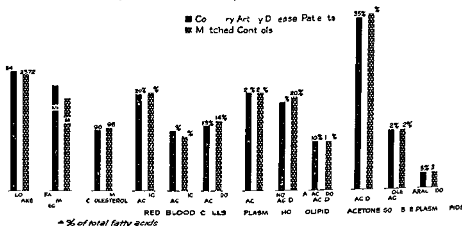


Fig 31 James A T Lovelock J E Webb J and Trotter W R (430) Note that the clinically normal and coronary disease patients have similar patterns of blood fatty acids including essential fatty acids

Undoubtedly, work in the years immediately ahead will effectively clarify this group of problems concerning the unsaturated vegetable oils and essential fatty acids Irrespective of the ultimate resolution of these questions the demonstration of an effect of dietary unsaturated oils on serum cholesterol levels represents one of the important advances of recent years By deepening and refining our knowledge it has significant ly reinforced the nutritional metabolic cholesterol lipid lipotrotein theory of atherogenesis It is also of great practical meaning (see below)

In summary then the recent findings of clinical pathological research have amply demonstrated a close relationship between level of choles terolemia and development of atherosclerotic disease on the one hand, and between pattern of diet and level of cholesterolemia on the other The clinico-pathologic data parallel and complement the epidemiologic find ings

Chapter 5

Nutrition and Atherosclerosis (*Continued*)

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In species more resistant than the chick and the rabbit it proved possible to induce hypercholesterolemia and atherosclerosis by using more complex forms of the same fundamental nutritional metabolic alteration

Thus, in the dog positive results were obtained by feeding a high-cholesterol, high lipid diet combined with hypothyroidism, in the monkey and the rat by feeding a high-cholesterol high lipid diet combined with a nutritional deficiency of the sulfhydril containing amino acid methionine (1 453–458) More recently hypercholesterolemia and atherosclerosis were produced in monkeys and rats with high fat high cholesterol diets alone (457 459 460)

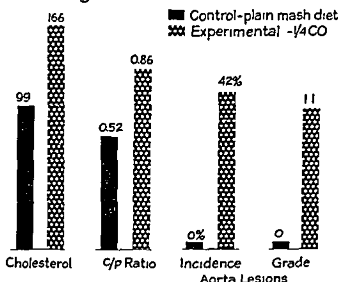


FIG 32 Stamler J and Katz L N (452) Here and in subsequent figures the symbol C is for cholesterol O for oil ¼ CO is ¼ per cent cholesterol + 5 per cent cotton seed oil in chick starter mash the symbol O without a numerical prefix is 5 per cent cottonseed oil throughout Unless otherwise indicated all groups had similar patterns of feed-caloric intake growth and development Here and in subsequent figures plasma cholesterol levels are in mg per cent aorta lesions are gross plaques in the thoracic aorta incidence is the percent of birds per group with lesions grade is the average grade of lesions in birds with lesions grading is on a scale of 0 to 4 (*cf* ref 1)

Moreover coronary thrombosis and myocardial infarction were recently induced in rats by dietary means This was accomplished by giving rats thiouracil and a diet containing 5 per cent cholesterol 2 per cent sodium cholate and 40 per cent butter fat (or 20 per cent Crisco + 20 per cent cod liver oil) for 14 weeks Coronary thrombosis and myocardial infarction occurred in 20 per cent of the animals Marked lipid accumulation was observed in the coronary arteries but not atherosclerosis When 40

per cent fat was given in the form of 20 per cent corn oil plus 20 per cent Crisco coronary thrombosis and myocardial infarction did not supervene (see previous and subsequent discussion on unsaturated oils) (462) Another investigator induced calcified atheromas and coronary occlusion by a combination of nutritionally induced hyperlipemia and vascular injury (463 464) These accomplishments go a long way toward meeting a longstanding major challenge to atherosclerosis research

3 *Dietary Cholesterol and Lipid in Experimental Atherogenesis* —In viewing this research development in perspective it is essential to appreciate the common thread running through all these achievements Invariably the *sine qua non* for experimental atherogenesis was a nutritional

EFFECTS OF DEFATTED MASH IN
CHOLESTEROL-FED COCKERELS

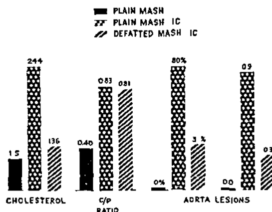


Fig 33 Stamler J Pick R and Katz L N (471) Note the minimal hypercholesterolemia and atherogenesis in chicks fed 1 per cent cholesterol in fat extracted mash

alteration the critical change being to a high fat high cholesterol intake maintained over a sustained period and leading to a hypercholesterolemic hyperlipemia With a few exceptions (see below) dietary excess of both cholesterol and neutral fat played a key role in all species studied This combination of the two appeared to be decisively important Thus excess cholesterol feeding in the complete absence of neutral fat and excess neutral fat feeding in the complete absence of cholesterol tended to be minimally atherogenic (Fig 33) (1 461 465 471) Further at a given level of excess dietary chole terol atherogenicity tended to rise as neutral fats—either unsaturated vegetable oils or saturated animal fats—were added in increasing amounts Without this combined cholesterol lipid nutritional aberration other changes in diet were by themselves generally not atherogenic

Several partial exceptions to the foregoing statements have emerged from recent studies Thus, moderate hypercholesterolemia and atherosclerosis may develop in animals on a cholesterol free diet—in ground squirrels (hibernators) after 3 to 18 months on an *ad lib* fattening diet high in vegetable lipid from peanuts (466), in geese after 3 months on a forced fed, high carbohydrate, fattening regimen—a diet rendered far more atherogenic with addition of cholesterol (467), in rabbits after 12 months on an *ad lib* diet high in vegetable fat from peanuts (468), in rabbits after 100 days on a purified ration containing 20 per cent highly saturated hydrogenated coconut oil (469) The published reports, which are available on the first three of the above studies indicate that atherogenesis was relatively slight to moderate on these non-cholesterol containing regimens, in marked contrast to the extensive, severe lesions developing rapidly in cholesterol lipid fed rabbits or fowl These data suggest that hypercholesterolemia and atherosclerosis may be induced—to a limited extent in some species at least and after relatively long time periods—by excessive intake of calories *per se*, even when derived from carbohydrates and/or unsaturated vegetable oils, without cholesterol or animal fat * They further suggest that highly saturated fat without cholesterol may induce hypercholesterolemia and atherogenesis, at least in rabbits even without concomitant development of obesity Finally, they support the significant conclusion that *prolonged ingestion of a diet combining excess of cholesterol lipids† and calories has particularly pernicious hypercholesterolemic and atherogenic effects This is the typical contemporary American diet*

4 *Diet induced Reversibility of Experimental Atherosclerosis* —Another major early contribution of experimental atherosclerosis was the demonstration that the atherosclerotic plaque is, within limits a reversible lesion This was shown in rabbits chicks and dogs (1, 451, 470, 472–474) Hypercholesterolemia and atherosclerosis were first produced by feeding an atherogenic diet upon withdrawal of this diet and substitution of a low fat low cholesterol ration hypercholesterolemia and atherosclerosis underwent gradual regression

Earlier studies of this type were confined to analyses of lesions in the aorta Recently it was clearly demonstrated that coronary lesions were also reversible by dietary and other means (see below) (1, 472 473)

5 *Unsaturated Vegetable Oils—Essential Fatty Acids* —The recent work on the effects of unsaturated vegetable oils on cholesterolemia in man led to exploration of this problem in experimental animals *Before* consideration of the newer findings it is worth noting that for decades experimental atherosclerosis was routinely produced—originally in rab

*The interpretation of these animal-experimental findings in relation particularly to the recent observations on unsaturated oils *vs* saturated fats in man must be regarded as *sub judice* pending additional data This problem is discussed further below

†See preceding footnote

bits and latterly in chicks and other animals—utilizing diets containing cholesterol plus unsaturated vegetable oils In apparent contradiction to the limited findings of supplementation studies in man (see above), the incorporation of large amounts of unsaturated vegetable oils in the high cholesterol diets of experimental animals did not inhibit hypercholesterol emia and atherogenesis (1, 451) In fact it is an old observation in rab bits and chicks that ingestion of mash supplemented with cholesterol plus vegetable oil resulted in more marked hypercholesterolemia than feeding

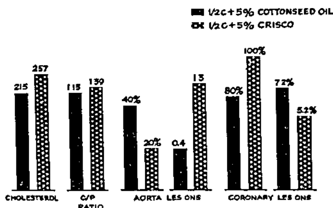


FIG 34 Stamler J Pick R and Katz L N (476) Note the essentially similar findings in the two groups despite the marked differences in amounts of saturated fat and essential fatty acids in the two rations

mash plus cholesterol alone (1) Thus, hypercholesterolemia and athero genesis were minimal when cholesterol was fed with defatted mash *i e* mash presumably deficient in essential fatty acids (Fig 33) (471) Further as already noted above rations high in unsaturated vegetable fats (*e g* from peanuts) may induce hypercholesterolemia and athero sclerosis in rabbits and squirrels in the complete absence of dietary choles terol (468) Moreover, feeding mash plus 20 per cent cottonseed oil alone (without cholesterol) apparently induced slight hypercholesterolemia (1) Again these are results in apparent contradiction to those in man

Recent experiments showed that feeding chicks 1 per cent cholesterol mashes supplemented with varying lipids at the 5 to 10 per cent level—*e g* relatively saturated lard or hydrogenated vegetable fat *vs* unsatu rated vegetable oils (linseed cottonseed corn oil or a linoleic acid con

5

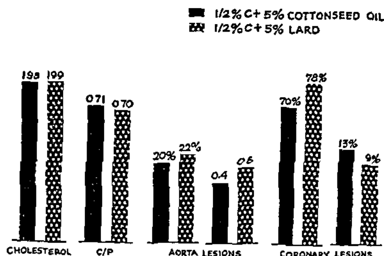


FIG 35 Stamler J Pick R and Katz L N (476) Note again the essentially similar findings in the two groups

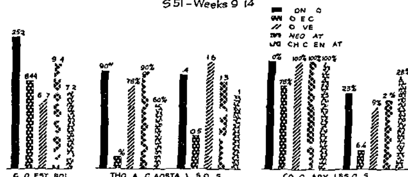


FIG 36 —Stamler J Pick R and Katz L N (477) All groups received 1 per cent cholesterol + 10 per cent fat In the control group the fat was cottonseed oil The oleic acid concentrate was 94 per cent oleic 1 7 per cent linoleic acid the olive oil was 86 per cent oleic 6 per cent linoleic the Neo fat was 73 per cent oleic 12 per cent linoleic the chickenfat was 52 per cent oleic + vaccenic 17 per cent linoleic acids The results of this experiment were somewhat unusual in that the group receiving oleic acid had significantly less aorta and coronary atherogenesis than the other groups despite similar marked hypercholesterolemia It is not clear why this one group on a high oleic acid diet exhibited these findings different from the other groups receiving like amounts of other preparations high in oleic acid Feed intake and rate of weight gain were similar in all groups

centrate)—yielded little or no differences in hypercholesterolemia and atherogenesis (Figs 34 to 36) (461, 476, 477) Similarly addition of a linoleic acid concentrate to a mash containing powdered egg yolk also failed to suppress hypercholesterolemia and atherogenesis Comparable experiments of other investigators in rabbits and chicks generally—with few exceptions—yielded similar results (482–494 *cf* also refs 478–481) Further with cottonseed or corn oil at the 20 per cent level hypercholesterolemia and atherogenesis were markedly enhanced in cholesterol fed chicks (461, 476 477)

Similar extensive exprimments with several oils and combinations of oils have recently been carried out by a research group utilizing rats fed cholesterol + cholic acid (495 496) Their data led them to the following interpretation considerably different from the trend of thinking extant concerning the findings in man The non essential unsaturated fatty acids (oleic *et al*) promote hypercholesterolemia in rats on this regimen In contrast hypercholesterolemia is counteracted by both saturated and essential fatty acids The product dietary EFA (linoleic and arachidonic acids) times dietary saturated fatty acids has a high degree of negative correlation with the serum cholesterol values—and EFA and saturated fatty acids are equally active substituting for each other in inducing this anti hypercholesterolemic effect It is suggested that these relationships may be valid for man This hypothesis remains to be explored in further studies

On the other hand in a rabbit experiment of different design utilizing a purified cholesterol free ration it was observed that highly saturated hydrogenated coconut oil (20%) induced hypercholesterolemia and atherogenesis whereas unsaturated safflower oil had no such effect (469 *cf* ref 477) Further as already noted 40 per cent fat in the form of 20 per cent corn oil plus 20 per cent Crisco failed to induce coronary thrombosis and myocardial infarction in cholesterol thiouracil cholate fed rats—in contrast to 40 per cent butter fat (462)

In calling attention to the apparently divergent results of experiments with unsaturated vegetable oils in man *vs* chick rat and rabbit it is essential to note the differences in experimental design Except for a few studies in South African Bantus the human subjects investigated were individuals on American type high calorie high fat high saturated fat high cholesterol diets In association with these habitual diets most subjects exhibited moderate or marked hypercholesterolemia Most of the studies in such people were of the complete substitution type involving withdrawal of saturated animal fat and cholesterol and incorporation of unsaturated vegetable oil These investigations were patently not analagous in design to the aforementioned animal experiments The latter involved addition of cholesterol and various fats to the low fat low cholesterol rations of rabbits rats and chicks originally exhibiting low normal serum cholesterol levels

It would seem that further experiments are essential in animals having a design similar to the human studies—including complete substitution, partial substitution, and supplementation experiments Until these are accomplished, it would be premature to attribute the seemingly disparate findings in animals and man to "species differences" It may yet be that in this new area of work, further experiments and deliberations concerning them will yield an intellectual advance effectively accounting for all the apparent discrepancies In any case, should species differences actually be demonstrated, their mechanism becomes an important problem *per se* (1)

In an earlier section of this book, a discussion was presented of the current hypothesis that atherosclerotic disease may be a resultant of essential fatty acid deficiency At this juncture, it is appropriate to deal with animal experimental evidence bearing upon this problem Obviously, from the foregoing experiments, atherosclerosis was readily produced in chicks and rabbits by cholesterol feeding—even in the presence of large amounts of high EFA unsaturated vegetable oils In fact, their presence in the diet was associated with enhanced hypercholesterolemia and atherogenesis These results supervened, despite the fact that the experimental animals exhibited no tissue deficiency of polyethenoic essential fatty acids (Fig 37) (493 494) Thus, they cast doubt upon the hypothesis that atherogenesis is a resultant of EFA deficiency

Here it is important to recall the experimental conditions required for the production of true essential fatty acid deficiency in animals As the original work over two decades ago demonstrated signs of EFA deficiency can be elicited only by accomplishing virtually complete removal of all fat from the diet (416–420 497) The incorporation of only slight amounts of any natural fat (animal or vegetable) in the experimental ration rendered *impossible the production of signs of EFA deficiency*

Recently it was shown that EFA deficiency was more readily and rapidly produced when a diet rigidly devoid of lipid was combined with other nutritional metabolic abnormalities *e g*, high cholesterol intake induced diabetes mellitus, or other stresses (498–503) These findings suggested that EFA need may be a function of the overall nutritional metabolic situation of the organism This phenomenon of variability in the need for dietary essentials—dependent upon other nutritional metabolic factors—has also been demonstrated in experimental animals for such nutrients as methionine vitamin B_{12} folic acid choline tocopherols and pyridoxine This may be of considerable practical and theoretical importance particularly in view of data suggesting a role for the e metabolites in the regulation of cholesterol metabolism and atherogenesis (see below) (454 455, 458, 461, 504–511 513–539) These experimental findings lend indirect support to the imbalance hypothesis of atherogenesis (*see above*) (16 19 21, 22 461) Moreover they constitute animal experimental support for the conclu ion—already pre ented above in the section on

clinical investigation—that if an EFA deficiency does in fact exist with ingestion of diets high in calories, total fats saturated fats, cholesterol, then it can only be a relative, secondary, derivative deficiency

6 *Corn Germ, Sitosterols, Dihydrocholesterol, Brain Extracts* —In one recent study on the effects of various corn oil preparations in cholesterol fed chicks it was demonstrated that incorporation of whole corn germ yielded highly effective inhibition of hypercholesterolemia and atherogenesis (486) This finding was confirmed in subsequent studies in our

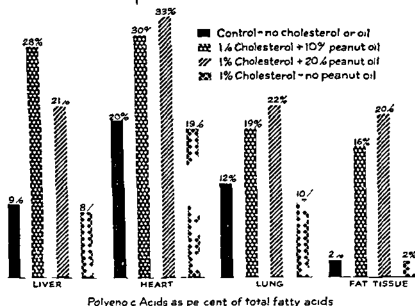


Fig 37 —Dam H Kristensen G Kofoed N Prange I and Sondergaard E (494) Note that the two groups receiving cholesterol + peanut oil had tissue levels of essential fatty acids greater than those of the control group Note also that the group receiving 1 per cent cholesterol without peanut oil had levels of tissue EFA similar to the controls Thus no evidence of reduction in tissue EFA *i e* of EFA deficiency was noted in these cholesterol fed birds

laboratory (540) The mechanism of this phenomenon is apparently related to the lack of fat absorption of the whole germ Whole corn germ has its oil so enclosed that it is not available for absorption It therefore acts like a low fat diet

Several years ago it was demonstrated that the incorporation of sitosterols in the diets of cholesterol fed chicks and rabbits resulted in marked suppression of hypercholesterolemia and atherogenesis (Fig 38) (1, 541–552) Large amounts of plant sterols were necessary to achieve this effect

the ratio to dietary cholesterol being 1–7 1 This action was attributed to inhibition of intestinal absorption of cholesterol possibly due to formation of a poorly soluble mixed crystal of cholesterol and sitosterol (553 559) This conclusion was supported by the observation that sitosterols failed to reduce hormone induced endogenous hypercholesterolemia, resulting from administration of estrogens or hydrocortisone to chicks (552) Limited data indicated that sitosterols were also ineffective in speeding up the mobilization of previously accumulated tissue cholesterol *i e*, they were effective only prophylactically, but not therapeutically (560, 561)

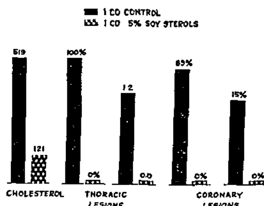


Fig 38 Stamler J Pick R and Katz L N (552) Note the virtually complete inhibition of hypercholesterolemia and atherogenesis in the group receiving plant sterols

Dihydrocholesterol was also shown to block diet induced hypercholesterolemia and atherogenesis in chicks rats and mice However when fed for long periods of time, this sterol was itself absorbed in sufficient quantities to produce elevated plasma levels and lesions This was also true for lanosterol and delta 4 cholestenone With the exception of one report these phenomena were not observed to occur to any significant degree with ingestion of plant sterols (562–571)

Results similar to those obtained with plant sterols were noted following the administration of defatted brain extract preparations (572–576)

7 *Nutritional Interrelationships in Experimental Hypercholesterolemia and Atherogenesis* —A highly significant development in experimental atherosclerosis research in recent years has been the undertaking of studies on the interrelated effects among cholesterol lipid and other nutrients (454, 455, 458, 461 504–511, 513–529, 537–539 577–597) For example it was demonstrated that hypercholesterolemia and atherogenesis were ap

parently aggravated in cholesterol oil fed chicks permitted to ingest only 60 per cent of their usual total feed intake, or subjected to intermittent starvation (Fig 39) (1, 577 578 also *cf* ref 510, 579)

Further, as already noted it was shown that hypercholesterolemia and atherogenesis could be successfully produced in monkeys and rats by utilizing a ration high in cholesterol lipid and inadequate in the sulfhydril containing amino acid methionine (1, 453–458, *cf* refs 252 511, 513–516 521, 527, 537 580–582) This phenomenon was amply confirmed in experiments in chicks (Fig 40) (461, 504–509)

EFFECTS OF DIETARY RESTRICTION
IN CHOLESTEROL-FED COCKERELS

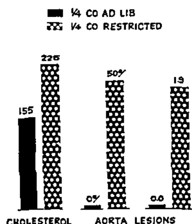


FIG 39 Rodbard S Bolene C and Katz L N (577) Note the more marked hypercholesterolemia and the earlier emergence (19–24 weeks) of atherosclerotic lesions in the group receiving a diet of similar composition to the control but restricted in amount to 60 per cent of the control group s feed intake

Other studies showed that feeding a ration low in choline also aggravated the hypercholesterolemic and atherogenic effects of a high cholesterol high fat diet in rats (286 463 524–526 537 539) (In contrast to these findings with deficiency of methionine and choline experiments in recent years tended generally—with few exceptions—to confirm previous observations that supplementation of an adequate ration with lipotropic factors failed to suppre s hypercholesterolemia and atherogenesis [1, 12–14])

In subsequent experiments it was shown that hyperlipemia hyper cholesterolemia and atherogenesis were aggravated in cholesterol oil fed chicks ingesting a diet low in total protein In one such study sucrose was incorporated in the diet at the expense of protein, so that total pro-

EFFECTS OF A METHIONINE-DEFICIENT DIET ON CHOLESTEROL-FED COCKERELS

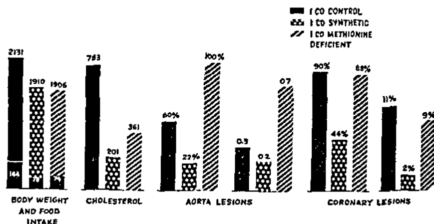


Fig 40 Stamler J Pick R, and Katz L N (505) The chicks on synthetic diet had a ration of purified constituents adequate in known nutrients The experimental group (1 CO methionine deficient) had a similar ration except that a soy protein of low methionine content was fed and supplementary methionine was excluded from the diet Here and in subsequent figures body weight is the terminal weight in grams feed intake is in grams per bird per day Note the more marked hypercholesterolemia and athero genesis in the methionine deficient group compared with the group on an adequate synthetic ration Note also the significantly less marked hypercholesterolemia and atherogenesis in the 1 CO synthetic group compared with the 1 CO control on com mercial mash This may be due to the higher protein content in the diet of the former (35 per cent *vs* 20 per cent)

Effects of addition of refined Carbohydrates to High Fat, High-Cholesterol Chick Mash with and without reduction of Dietary Protein

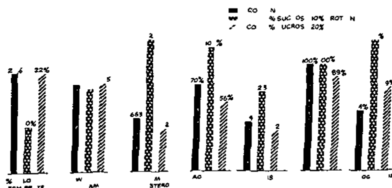


Fig 41 Stamler J Pick R and Katz L N (506) The third group—1 CO 45 per cent sucrose 20 per cent protein—received purified soy protein in order to increase the dietary protein to 20 per cent Note the intensified hypercholesterolemia and athero genesis in the group with reduced protein intake due to incorporation of 45 per cent sucrose in the atherogenic mash Note that this was prevented by addition of protein

tein was reduced from the usual 20–25 per cent to 10–15 per cent * Another group of chicks received a similar high level of sucrose ("empty calories" from carbohydrate), but with purified soy protein added to maintain total protein at the 20 per cent level Unlike the high sucrose low protein group, this high sucrose, adequate protein group behaved similarly to the control group (Fig 41) (504 506) These data indicated

EFFECTS OF A HIGH VITAMIN-HIGH PROTEIN SUPPLEMENT TO A CHOLESTEROL-OIL-REGULAR MASH DIET

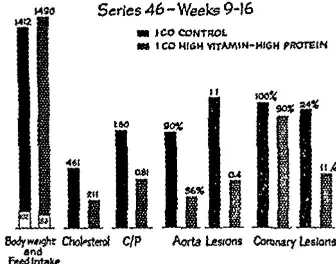


FIG 42 —Stamler J Pick R, and Katz L N (505) The protein supplement was at the 35 per cent level by weight and included 7 per cent of each of the following casein defatted fish meal soy protein defatted liver Brewer s yeast In addition to the vitamins of the Brewer s yeast individual vitamins were added to the mash at a level five times that used routinely in a synthetic ration Note that the protein vitamin supplement inhibited hypercholesterolemia and atherogenesis

that the protein content of the diet—not its sucrose content—was the decisive factor *influencing the cholesterolemic and atherogenic response* to the high fat, high-cholesterol intake Recently other workers reported that the quantity and type (glucose *vs* sucrose) of refined carbohydrate in an experimental or human ration may influence the cholesterolemic response (516, *cf* also ref 372)

In other related experiments it was demonstrated that high protein, high vitamin supplementation suppressed hypercholesterolemia and atherogenesis in cockerels ingesting either a purified or commercial ration high in cholesterol and fat (Figs 42 to 44) (504 505 507) In studies on the mechanism of this phenomenon it was shown that vitamin supple

*In the diets of most Americans proteins supply 12 to 14 per cent of calories (22 23 107 197 210–214 238)

EFFECTS OF HIGH VITAMIN–HIGH PROTEIN VS HIGH PROTEIN ALONE IN CHOLESTEROL-FED COCKERELS
S-47 Weeks 13-23

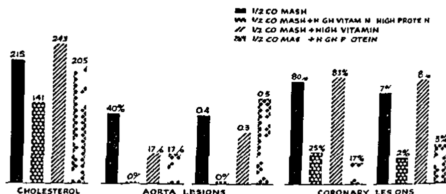


FIG 43 Stamler J Pick R and Katz L N (505) The vitamin and protein supplements were the same as those in the experiment illustrated by Fig 42 Note that combined high protein high vitamin supplementation was most effective in inhibiting hypercholesterolemia and atherogenesis Note that high vitamin alone was ineffective and that high protein alone was partially effective

Effect of adding Casein and Egg Albumen to Mashes containing Butter + Cholesterol and Egg Yolk respectively
-S-50 12 to 18 weeks

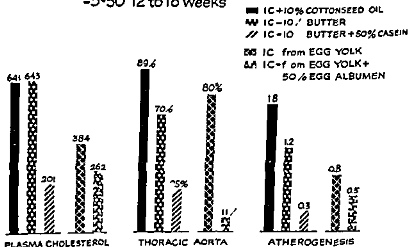


FIG 44 Stamler J Pick, R and Katz L N (507) Note that supplementation of both atherogenic rations *with casein and egg albumen respectively had a significant* inhibitory effect on hypercholesterolemia and atherogenesis Note also that hypercholesterolemia and atherogenesis tended to be more marked in the group on 1 per cent cholesterol + 5 per cent cottonseed oil than in the cholesterol + butter and the egg yolk groups again demonstrating lack of inhibitory effects of unsaturated vegetable oils in chicks

mentation alone was without influence (Fig 43) * On the other hand, high protein alone apparently suppressed coronary atherogenesis in a manner similar to the high protein high vitamin combination (Figs 43 and 44) However, high protein alone apparently had less definitive and clearcut effects than combined high protein, high vitamin supplementation These findings suggested that the high protein diet was the decisive factor responsible for the results but that high vitamin intake may have had an adjuvant, synergistic influence These results constituted the first demonstration of an anti atherogenic influence of dietary protein They were consistent with several concurrent independent reports on the effects of protein supplementation on hypercholesterolemia in cholesterol lipid fed animals (511, 513, *cf* also refs 510 514–516 520 580 582) †

In addition to the foregoing experiments on nutritional interrelationships, the last year or two witnessed the development of studies on the effects of minerals in animals on a high fat, high cholesterol diet Thus, evidence was obtained indicating that cobalt magnesium and vanadium may inhibit hypercholesterolemia and atherogenesis (518–520 584 585)

It should be emphasized that all these experiments on nutritional interrelationships represent analyses of the effects of specific nutrients (proteins vitamins carbohydrates minerals and other nutrients) in animals on high fat, high cholesterol diets By demonstrating significant influences of some of these nutrients (*e g* proteins) the e experiments lend support to the imbalance hypothesis elaborated above At the same time their results reinforce the basic tenet of the nutritional metabolic cholesterol lipid lipoprotein theory of atherogenesis—*i e* that high fat, high cholesterol intake is the decisive nutritional aberration in the causation of hypercholesterolemia and atherogenesis

*Previous studies by our group had shown that addition of large amounts of vitamins B_1 and E had no effect on cholesterolemia and atherogenesis in chicks fed high fat high cholesterol diets Imbalance studies on the combined influences of various vitamin deficiencies in birds on similar atherogenic diets are currently in progress Other workers have reported that large doses of nicotinic acid (538 586–594) pyridoxine (595) or tocopherols (596) may lower serum cholesterol levels in man Work has also been done in guinea pigs on combined vitamin C deficiency and cholesterol feeding (528 583 597) and on B_{12} B and pantothenate deficiency (517 521 523 529)

†A recent study indicated that varying the level of dietary protein had no effect on cholesterolemia in persons on a high fat diet (252)

Chapter 6

Hormonal and Other Endogenous Factors and Atherosclerosis

A The Key, But Not Exclusive Role, of Diet in Atherogenesis, Interrelationships Between Diet and Other Factors (Heredity, Physical Activity, Stress, Endocrine Function, Smoking, and the Like)

THE nutritional metabolic cholesterol lipid lipoprotein theory of athero genesis *therefore emphasizes the decisive—but not exclusive—role* of diet in the causation of this disease Since the development of disease in individuals is in fact influenced by an interplay between diet and other factors including endogenous factors then the delineation of these factors becomes one of the decisive tasks of research in this field

Extensive evidence has been available for many years—particularly from clinical research—concerning the atherosclerosis potentiating effects of diabetes mellitus hypothyroidism renal disease and essential familial hypercholesterolemic xanthomatosis (1) Similarly it has been abun dantly demonstrated—by epidemiologic clinical pathological and animal experimental work—that *hypertension* markedly increases the risk of atherosclerotic disease particularly when the prerequisite derangement in cholesterol lipid lipoprotein metabolism is also operative (Figs 18 and 48) (1–5 12–14, 21–23 69 71 90 96 107 112 125 126 134–137 143, 196–203 208 209 228–230 260–272 278 294 314 315 436 444–448, 461 632 647–650)

It is essential to re emphasize that we attribute a *key*—but not exclusive—role to diet *We in no way imply that atherosclerosis is purely* and simply a dietary disease Such a viewpoint is definitely at variance with well established facts and therefore quite untenable Thus the fact that many individuals eating a typical American diet for decades reach old age without clinical evidence of atherosclerotic disease—this fact alone refutes any attempt to imply a one to one cause and effect relation ship between diet and disease Further the marked sex differential—the high incidence of coronary disease in middle aged American males in contrast to females—almost certainly contravenes any pure and simple dietary concept Similarly, the greater incidence of atherosclerotic dis-

ease in persons with diabetes, nephrosis hypothyroidism or hypertension contradicts any exclusvie dietary concept Actually, no serious scientist is making any such futile attempt to "fit" all the phenomena of athero sclerotic disease into the confines of a pure and simple dietary "explan ation

Obviously, as extensive clinical and experimental data demonstrate the nature of the organism plays an important role in determining the effects of life span ingestion of a potentially atherogenic diet Hence,

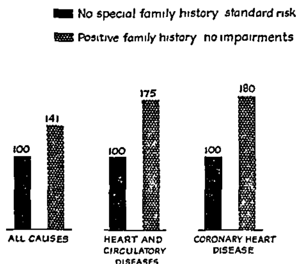


FIG 45 Lew E A (183) These data indicate that familial factors possibly hereditary and genetic influence the occurrence of atherosclerotic disease in individuals from population groups ingesting an habitual diet high in total calories total fats saturated fats cholesterol

different individuals ingesting similar habitual diets exhibit different levels of cholesterolemia In these individuals many factors may inter act significantly with diet—genetics and heredity metabolism and endo crinology clotting mechanisms previous medical history psychological make up and physical condition (fatigue stre s tension frustration and other conditions) environmental factors (smoking habitual physical activity of work urbanization and other factors) (Figs 45 and 46) (1–6 10–14 23 71 113 148 149 159 202 275 300, 322 446 451, 598–623 625–645 785) Antecedent allergic or infectious disease for example—possibly by damaging vessels and setting up sites of predilection for atherogenesis—may be of great importance in some cases Hypertension,

hypothyroidism, renal dysfunction, diabetes, certainly tend to potentiate atherogenesis (1) The evidence is considerable that estrogenic secretion in women has an opposite effect (ee below) (645, 646)

In recent years, great interest has been aroused concerning the possible influences of psychological stress and physical activity on the development of atherosclerotic disease, particularly coronary heart disease Up

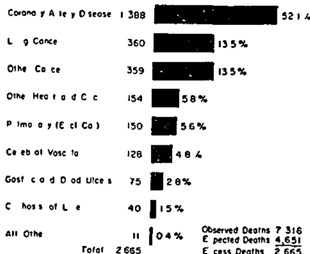


FIG 46 Hammond E C and Horn D (623 624) A total of 187 783 men aged 50–69 in 1952 were followed with almost 12 000 deaths occurring in 5 years The age adjusted death rate for all causes of the regular cigarette smokers was 68 per cent higher than that of the group who never smoked with a total of 2 665 excess deaths in the smokers Of these 2 665 excess deaths 1 388—52 1 per cent—were due to coronary artery disease The coronary disease mortality rate of these regular cigarette smokers was 70 per cent higher than that of those who never smoked These data suggest that smoking increases the risk of coronary disease in middle aged males habitually ingesting a diet high in calories total fats saturated fats cholesterol (Compare the findings of other recent epidemiologic studies—ref 2 also data on smoking and lipids-lipoproteins—ref 626 and a discussion of the whole problem of the interrelationship among diet smoking and coronary artery disease—ref 113)

to the present few data have been reported concerning the first of these (1–6 11–14 23 71 113 300 451 607–615 617–622 636–638 785)—an understandable fact in view of the complex and difficult problems of objective mensuration

Data were reported from Great Britain concerning physical activity Comparisons were made of sub groups within relatively homogeneous

socio-economic strata of the British population The e indicated that the incidence of coronary heart disease tended to be lower in the subgroups habitually engaged in greater physical activity at work Data along these lines were obtained in comparisons of sedentary bus drivers *vs* active bus conductors, sedentary telephone operators *vs* active postmen and other

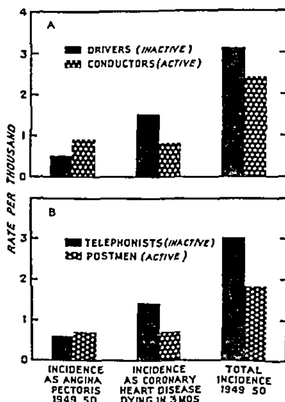


FIG 47 Morris J N Heady J H Raffle P H B Roberts C G and Parks J W (148) These data ind cate that the incidence of coronary disease (nonfatal and fatal) is lower in active than inactive workers in Great Br tain i e in a population ingesting an habitual diet moderately high in total calories total fats saturated fats cholesterol

similar comparisons (Fig 47) (25 148 598) However further studies by the same British group tended to cast doubt upon the significance of these observations (149) Moreover all strata of the population in Britain as in the United States and Norway—irrespective of socio-economic status and habitual physical activity of work—were found

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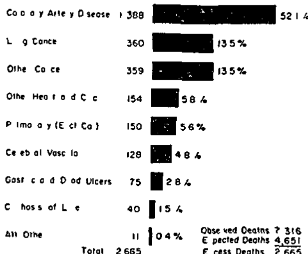


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atherogenesis *diet is the decisive factor* Thus, it would seem valid to designate diet as virtually a *sine qua non* for atherosclerosis and atherosclerotic disease even as the tubercle bacillus is a *sine qua non* for tuberculosis—although patently a multiplicity of host and environmental factors (nutrition and other socio economic variables) enter into complex interrelationship with the bacillus to influence the developmental patterns of the disease For without the habitual ingestion of a potentially atherogenic diet, clinical atherosclerotic disease would be rare among the middle aged members of any population, irrespective of the operation of other potentially offensive factors

INTERRELATIONSHIPS BETWEEN HYPERTENSION AND ATHEROGENESIS IN COCKERELS

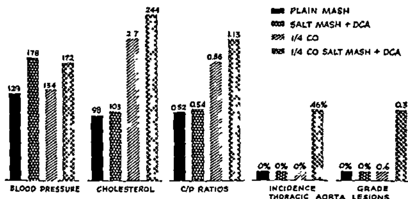


FIG 48 Stamler J Pick R and Katz L N (647) Stamler J and Katz L N (648) Note that hypertension failed to induce atherosclerosis in normocholesterolemic cockerels on a non atherogenic diet Note also that in this experiment a diet of ¼ CO for only 15 weeks (*cf* Figs 32 and 39) leading to moderate hypercholesterolemia failed to induce gross lesions in the thoracic aorta However the combination of blood pressure elevation plus the ¼ CO diet resulted in frank atherosclerosis

It should be noted that this conclusion has as its cornerstone the concept that the pathological lesion atherosclerosis is the prerequisite for clinical coronary heart disease in at least 90 per cent of cases (1 290 291 292 294 299 300) As is well known however morphologic atherosclerosis frequently exists without clinical disease What factors are responsible for the qualitative change from occult (pre clinical) to clinical disease? What are the causes of thromboses on plaques or hemorrhages into plaques leading to infarction? Unquestionably, part of the answer is quantity—the severity and extent of atherosclerosis (1, 290, 291 292 294 299 300) But it is unlikely that this is the whole answer Thus as already indicated diet may play a role here as well e g the fat content of the diet via its possible tendency to increase blood coagulability

to manifest high coronary heart disease incidence rates (*2, 6, 10, 19, 21–23, 71, 125 126, 134–137, 143, 150–154, 160, 172–180, 196, 197, 199, 208, 209, 228–230, 232–237, 260–273, 278*)

Correspondingly, recent observations indicate that epidemiologic patterns of cholesterolemia and atherosclerotic disease were more decisively influenced by diet than by level of physical activity at work (see foregoing figures) Thus in South African Bantu—with a habitual diet low in total fats, saturated fats, cholesterol—the level of cholesterolemia and the incidence of coronary disease were found to be low in both sedentary and active workers (Fig 4) (4–6, 21–23, 71, 72, 91, 107, 119–121, 123) Similar observations were also reported from Japan and Italy (Fig 8) (72, 91, 107, 116–118 133) Contrariwise, in Sweden and Finland—with a habitual diet high in total calories, total fats saturated fats cholesterol—level of cholesterolemia and incidence of coronary disease were observed to be high in both sedentary and active workers (72, 107 157–160) Similarly recent studies in the United States consistently revealed a high level of cholesterolemia and a high prevalence and incidence of coronary disease in all sectors of the middle aged male labor force, irrespective of nationality, socio economic status, income occupation, physical activity of work, urban or rural residency (*1, 2, 6 10 12–14, 21–23, 71, 72, 105–*109, 111, 112 125, 126 133–137 143 172–180 196, 197, 199, 208, 209, 228–230 232–237 251 260–273 278–281 645)

These data impressively support the concept that diet is the decisive variable determining the pattern of atherosclerotic disease in a *population* Nonetheless studies on the interrelationships among nutrition physical activity atherosclerosis and atherosclerotic disease—particularly in countries where large segments of the population ingest high calorie high fat high cholesterol diets and lead a relatively sedentary life—are still limited Recent studies indicate that physical activity may prevent an increase in serum cholesterol, under circumstances when increased fat is ingested to meet greater caloric need (*322, 599, 639*) It has also been suggested that continued physical activity through middle-age may be a possible factor in the prevention of atherosclerotic disease (640) Further work is therefore certainly indicated on the effects of large muscle activity in persons and groups ingesting potentially atherogenic diets

With respect to the individual therefore, the relationship between diet and other factors may be properly formulated as follows based on our present knowledge In the individual member of a population group habitually ingesting a potentially atherogenic diet the development of morphologic atherosclerosis and atherosclerotic disease is influenced by multiple factors There is a complex interplay between diet and other factors which operate to accelerate or to retard atherogenesis Thus, it is not a matter of one factor to the exclusion of others it is not a matter of either or But, among these multiple factors interacting *to influence*

—also stimulated concern with this field of re earch This entire area is at present in process of active development including exploration of its therapeutic implications (see below)

C Thyroid Hormone

Of the endocrine glands attention has been focussed for years on the thyroid The original basis for this concern was the clinical pathological observation that cholesterolemia and atherogenesis were increased in hypothyroidism and decreased in hyperthyroidism (1, 688) These findings were supplemented with extensive experimental evidence in cholesterol fed rabbits chicks and dogs of an interrelationship among thyroid hormone cholesterol metabolism and atherogenesis (1 3 687) Recent years have witnessed only limited activity in this area of research on atherosclerosis (see below)

D Estrogens

The influence of ovarian estrogenic secretion has been a particular center of contemporary research attention (1 3–5 12–22 461 645 646, 689) This problem has been one of the major foci of our group during the past 8 years

1 *Background* —Two key sets of facts concerning human coronary heart disease served as a ba is for this work The first was the finding that groups of middle aged males with manifest coronary disease had significantly raised levels of both plasma cholesterol and cholesterol/phospholipid (C/P) ratio (Fig 19) (1 3–5 12–14 21 22 69 71 171 202, 279–281 283 301–318 645 689) The question arose whether one or the other of these changes played a more important role in atherogenesis

A second major stimulus was the demonstration of a marked human sex differential in susceptibility to coronary heart disease in the middle aged populations of the economically more developed countries (1–5 12–23 71 90 134–137 143 155 172–187 196–206 208 209 294 461 645 646 689) Numerous clinical and epidemiologic studies demonstrated a remarkable resistance of young and middle aged women to coronary heart disease—an immunity tending to disappear in the decades following the menopause At the time these investigations began no animal experimental data were extant accounting for this highly significant phenomenon It was a scientific enigma

2 *Prophylactic Experiments with Estrogens* —Attention was first focussed on the differences in patterns of hyperlipemia in chicks resulting from cholesterol feeding versus estrogen administration The former invariably produced a predominant disproportionate rise in plasma cholesterol a smaller increment of plasma phospholipids resulting in markedly *elevated* C/P ratio Estrogens on the other hand caused a manifold increase of phospholipids a considerably less marked elevation of choles

and thereby perhaps enhance risk of thrombogenesis (assuming that blood coagulability is related to pathologic thrombosis) (326–344) Nervous and hormonal factors—related to stress and strain in the individual—may exert an influence, possibly by affecting lipid metabolism, and/or coagulability possibly by increasing the risk of sudden arrhythmic (non thrombotic) death in cases where coronary atherosclerotic disease has led to ischemia and increased myocardial irritability (607–622)

Undoubtedly, this problem of factors precipitating acute episodes is highly complex and important, *but a problem secondary to the decisive one, atherogenesis*

B Blood Clotting and Fibrinolytic Mechanisms

Another important development of recent years has been the extended exploration of the relationships among anticoagulants blood clotting mechanisms, lipid metabolism atherogenesis and thrombus formation It is, of course a well established fact that thrombotic episodes are in a major way responsible for the conversion of subclinical atherosclerotic pathology to clinical disease *e g* coronary or cerebral thrombosis with infarction The importance of this problem resulted in extensive studies with anticoagulants soon after their biochemical identification This line of research received further impetus with the demonstration of the profound effects of heparin on cholesterol lipid lipoprotein metabolism (1 651–661 674 675) It was shown that this biological product has a remarkable ability to clear lipemic serum Heparin apparently activates a plasma enzyme system (a lipoprotein lipase) capable of markedly altering the spectrum of plasma lipoproteins Evidence has been presented suggesting that endogenous heparin may play a role physiologically in lipid metabolism and that this mechanism may be abnormal in atherosclerotic subjects (662–673)

Based on these findings experimental work was done on the effects of heparin on cholesterol induced hyperlipemia and atherogenesis in chicks and rabbits Limited inconsistent data suggested that heparin may suppress these phenomena presumably by virtue of its effects on lipid metabolism (676–684) Similar findings with dicumarol were also reported (1, 685) On the other hand an extended series of experiments in our laboratory consistently yielded negative results In fact the evidence indicated that both heparin and dicumarol may potentiate atherogenesis under certain experimental conditions (686)

Recently the additional observation was reported that ingestion of high fat meals induced a decreased fibrinolysis and an increased blood coagulability, measured *in vitro* (326–345) This finding further enhanced research interest in interrelationships among anticoagulants lipid metabolism blood coagulability fibrinolysis atherogenesis and thrombogenesis Correspondingly, the thrombogenic theory of atherogenesis (499, 450)—alternative to the dietary nutritional cholesterol lipid lipoprotein theory

that estrogen induced inhibition of coronary lesions may be closely inter linked in individual birds with maintenance of C/P ratios at or near nor mal levels (Fig 50) (1 645, 689–691)

Finally this initial study—by demonstrating that estrogens were capable of preventing experimental coronary atherosclerosis in cockerels—for the first time brought forward experimental evidence supporting the hypothesis that the sex difference in human susceptibility to coronary disease may be at least in part a resultant of ovarian hormonal secretion

EFFECTS OF ESTROGENS ON PLASMA LIPIDS
AND CORONARY ATHEROGENESIS
IN CHOLESTEROL FED COCKERELS

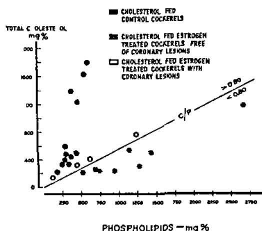


FIG 50 Pick R Stamler J Rodbard S and Katz L N (691) Note that all b rds free of lesions had cholesterol/phospholipid (C/P) ratios less than 0 80 *i e* at or near normal values

Subsequently it was demonstrated that oral administration of mixed conjugated equine estrogens was equally effective in producing feminiza tion altered plasma lipid patterns and prevention of coronary athero genesis Estrogen effects on plasma lipids and lipoproteins were also further delineated (1 645 689) Curiously estrogens apparently effected a significant reduction of α lipoproteins in cockerels a change precisely opposite to that induced in man (see below) Estrogen treated choles-terol oil fed chicks also exhibited apparent decreases in plasma low density β lipoproteins (of the S_f 20 to 400 class) and in plasma esterified/total cholesterol ratios

Several synthetic estrogens given at oral or parenteral dosage levels adequate to accomplish feminization also maintained normalization of C/P ratios and prevented coronary atherogenesis in cholesterol fed

terol, so that C/P ratio was significantly *depressed* below normal (Fig 49) (1, 645 689–691)

In the initial experiments, which were of the "prophylactic" type, estrogens were administered to cockerels simultaneously transferred to an atherogenic diet Estrogens in these cholesterol fed cockerels did induce a marked enhancement of phospholipemia with consequent maintenance of C/P ratios at or near normal levels (Fig 50) The hormone also fem

Effects of Cholesterol Oil feeding vs Estrogen administration on plasma lipids of cockerels

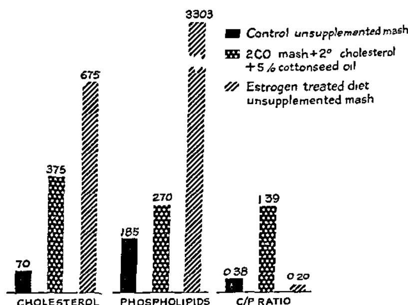


Fig 49 Stamler J Pick R and Katz L N (689) Stamler J and Katz L N (690) Pick R Stamler J Rodbard S and Katz L N (691) Note the predominant hypercholesterolemia in the cholesterol fed group with increase in the cholesterol/phospholipid (C/P) ratio Note the predominant hyperphospholipemia in the estrogen treated group with lowering of the C/P ratio

inized the cockerels as indicated by their combs and other secondary sex characteristics Gross examination after several weeks revealed the presence of marked atherogenesis in the *aortas* of both the estrogen treated and control birds However histological studies showed that the estrogen treated birds in contrast to the controls were practically free of lesions in the *coronary* arterial tree (Fig 50) This was an experimental demonstration of segmental differences in atherogenesis This observation, that different laws govern atherogenesis in different vascular beds, was supported by data on human material The data further suggested

and fibroblasts It was such relatively "young" plaques that estrogens completely reversed despite continued feeding of the atherogenic diet So thoroughgoing was this estrogen 'therapeutic" effect that special histological and histochemical studies revealed no deviations from normal (other than rare residual lipid infiltration) in the architecture of these coronary vessels—nor could any alterations be demonstrated in the ground substance (645 693)

This experiment proved once again that atherosclerotic plaques are, within wide limits partially and even wholly *reversible* Finally, this experiment—and particularly the special histochemical study accomplished in cooperation with our Argentine colleagues—yielded preliminary evidence suggesting that the estrogen anti atherogenesis may perhaps be related at least in part, to a reticulo endotheliosis

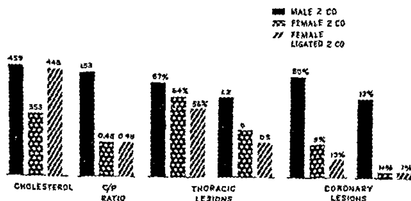


FIG 52 Stamler J Pick, R and Katz L N (695) Note that oviduct ligation resulted in similar levels of cholesterolemia in the male and female birds Note that both groups of hens had low C/P ratios reflecting estrogen induced hyperphospholipemia Note the minimal coronary atherogenesis in the hens In this experiment aorta atherogenesis was slightly less marked in the hens than in the roosters but the difference was not significant

4 *Effects of Endogenous Estrogen Secretion—Sex Differential in Chickens* —When sexually immature male and female chicks 8 to 15 weeks old were fed an atherogenic diet both sexes exhibited significant aorta and coronary atherogenesis—no sex differential in coronary atherogenesis was observed (1 645 694)

On the other hand egg laying hens in contrast to roosters of the same age were found to be remarkably resistant to cholesterol induced coronary atherogenesis, although both sexes were susceptible to aorta atherogenesis (Fig 52) (645, 689, 695)

cockerels On the other hand, studies with several synthetic estrogen analogues of low feminizing potency invariably yielded negative results (645)

3 *Therapeutic Experiments with Estrogens—Reversibility of Lesions* — In subsequent "therapeutic" experiments it was shown that estrogens were able to reverse cholesterol induced plaques in the coronary vessels of chicks *In fact, this anti atherogenesis supervened even when the atherogenic diet was continued during hormone administration* (Fig 51)

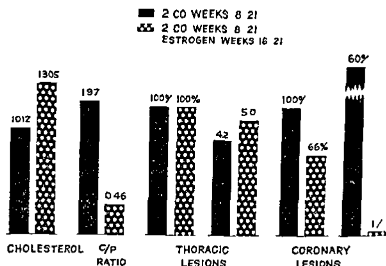


Fig 51 Pick R Stamler J Rodbard S and Katz L N (692) A third group not represented in this figure was sacrificed at 16 weeks of age after 8 weeks on diet and the presence of extensive coronary lesions prior to onset of estrogen therapy was thereby confirmed Note the marked reduction in coronary atherogenesis in the estrogen treated cockerels despite continued feeding of the potentially atherogenic diet

(1, 645, 689 692) *Estrogens reversed both the lipid and the fibroblastic components of these atherosclerotic plaques* This does not imply that estrogens were effective in removing areas of marked hyalinization advanced fibrosis, calcification or bone formation Such advanced lesions were not present in the control birds sacrificed after 8 weeks on the atherogenic diet Rather, their coronary vessels showed plaques composed only of actively proliferating fibroblastic tissue with moderate collagen deposition, plus lipid and cholesterol situated extracellularly and in lipophages

Estrogens were also combined with pancreatectomy, with administration of corticoids including desoxycorticosterone acetate (DCA) cortisone, hydrocortisone and ACTH Dosages of the latter were adequate to produce one or another manifestation of hyperadrenocorticism Hydrocortisone induced frank steroid diabetes (1 12–14 645 698) Neither pancreatectomy nor corticoids had any counteracting influence on estrogen anti atherogenesis (1 12–14, 645 698)

EFFECTS OF ESTROGEN PLUS ANDROGEN IN CHOLESTEROL FED COCKERELS

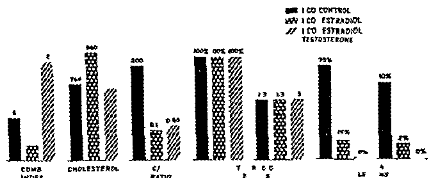


Fig 54 —Stamler J Pick R and Katz L N (697) Note in the birds receiving estrogen + androgen the masculinized comb index the maintenance of estrogen effects on C/P ratio and on coronary atherogenesis

More recently estrogen administration to cockerels was coupled with induction of hypothyroidism by thiouracil feeding thyroidectomy or thyroidectomy plus I[131] administration Hypothyroidism was associated with significant loss of the ability of estrogens to protect the coronary vessels against atherogenesis (Fig 55) (645 687) It was associated with a tendency to higher C/P ratios These findings are intriguing in view of the well known association among hypothyroidism hypercholesterolemia and atherogenesis in human beings

Finally a combination of insulin plus estrogens in cholesterol fed cockerels was undertaken because insulin counteracted the regression of atherosclerotic lesions usually occurring in cockerels following transfer from an atherogenic to a normal diet (645 689) The administration of the pancreatic hormone apparently counteracted the ability of estrogens to protect the coronary vessels against cholesterol induced atherogenesis (Fig 56) Further work is proceeding on this phenomenon * This finding

Very recently we have found that a combination of estrogen and a low protein diet (with or without added insulin) led to ulceration (and thrombosis and dissecting aneurysm) of the aortic lesions in the male chick (786) Still more recently such ulcerations were found to occur in the coronary vessels as well (787) Insulin addition was not essential for this ulceration to develop only estrogen and a low protein diet Further ulceration was found to occur during the healing stage of the lesions (787) Thus complications of the basic atherosclerotic process have been produced experimentally

However, the role of egg laying in the disposal of excess cholesterol lipid required analysis since cholesterol fed hens had somewhat lower plasma total cholesterol levels than their rooster counterparts (Fig 52) Surgical ligation of the oviducts was therefore accomplished so that mature ova were deposited into the abdominal cavity, and subsequently reabsorbed Such a group of oviduct ligated, egg producing cholesterol fed hens exhibited plasma cholesterol levels similar to those of an age and diet matched group of roosters These hens—while exhibiting marked aorta atherogenesis—remained almost completely free of coronary lesions (645, 695)

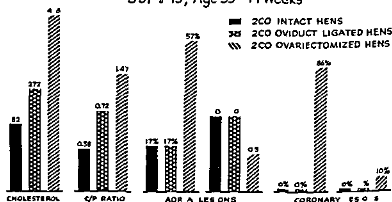


FIG 53 Pick R Stamler J and Katz L N (696) Note that ovariectomy resulted in aggravated hypercholesterolemia elevation of the C/P ratio and marked coronary atherogenesis

Finally surgically ovariectomized hens completely lacking endogenous estrogen secretion did in fact develop grossly elevated C/P ratios and extensive coronary atherosclerotic plaques in response to cholesterol feeding (Fig 53) (645 689 696) Ovariectomy had eliminated their immunity to cholesterol induced coronary atherosclerosis Therefore the resistance of mature egg producing hens to coronary atherogenesis is a product of ovarian function particularly estrogen secretion

5 *Effects of Estrogens Combined with Other Hormones*—The first experiment of this type utilized estrogen plus androgen in a 1 3 and 1 100 ratio (Fig 54) (1 12–14 645 689 697) With this combination masculinization of the major secondary sex characteristics of cockerels was readily maintained Concomitantly these birds exhibited full estrogenic effects on plasma lipid patterns and coronary atherogenesis Thus one of the triad of estrogen effects namely feminization, was counteracted while the other two continued to operate

an enhancement of hyperphospholipemia so that C/P ratios rose less markedly than in non-estrogen treated animals (645, 700 *cf* also refs 701, 702) These estrogen treated rats exhibited significantly less coronary atherogenesis compared with the controls

In our laboratory, studies of similar design were carried out in the herbivorous rabbit These experiments consistently yielded negative results irrespective of the variations in the level of cholesterol feeding and the route and amount of estrogen administration (Fig 57) (645, 689, *cf* refs 321 703) Estrogens in these rabbits failed to enhance hyper phospholipemia, so that C/P ratios were markedly elevated in contrast

EFFECTS OF ESTROGEN IN CHOLESTEROL-FED RABBITS —SERIES 1-4

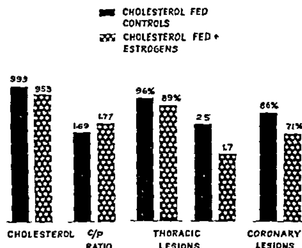


FIG 57 Stamler J Pick, R and Katz L N (689) Note in the estrogen treated rabbits the absence of any definitive hormonal effect on C/P ratio or atherogenesis

to the estrogen effects in chicks and rats Is there any cause-and effect relationship between estrogen failure to enhance hyperphospholipemia and failure to render the coronary vessels of rabbits immune to athero sclerosis?

7 *Estrogens Plasma Lipids Lipoproteins and Atherogenesis in Man* — During the years our department was unfolding the foregoing program of research on estrogens and cholesterol induced coronary atherosclerosis in chicks significant findings were published by other investigators on pos sible interrelationships among estrogens plasma lipids-lipoproteins and coronary atherogenesis in man (1 4 5 12-14 645, 646, 704-719) Thus it was established that estrogens exert a profound effect on human plasma

provoked the questions Is insulin one factor in the pathogenesis of the frequent, premature, severe atherosclerosis of diabetic patients? Is the diabetic woman's loss of "immunity" to coronary atherosclerosis a resultant, to any degree, of the effects of exogenous insulin?

6 *Effect of Estrogens in Mammalian Species* —Recently experiments were reported on rats maintained for 18 weeks on a regimen of estrogens plus an atherogenic diet Like chicks rats responded to estrogens with

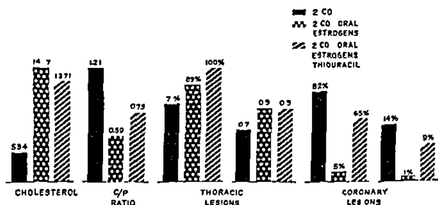


Fig 55 Pick R Stamler J and Katz L N (687) Note in the group receiving estrogens + thiouracil the tendency for C/P ratio to be higher and the more marked coronary atherogenesis compared with the group receiving estrogen alone

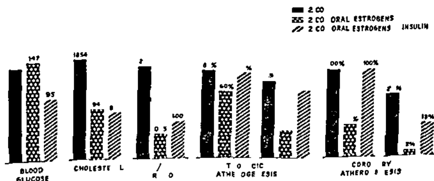


Fig 56 Stamler J Pick R and Katz L N (689) Note in the group receiving estrogens + long acting insulin (10–15 units/bird/day) the hypoglycemia and the more severe coronary atherogenesis compared with the group receiving estrogens only

Chapter 7

Definitive Approaches to Prophylaxis and Therapy of Atherosclerotic Disease in Man

A The Meaning of *Definitive Approaches*

By definitive approaches to prophylaxis and therapy are meant those which will retard arrest and even reverse atherosclerosis and its complications They are therefore, approaches for successful specific prevention or treatment of the clinical disease (21 645 720 721) These approaches are inevitably long term in nature

B Criteria for Evaluating Prophylactic and Therapeutic Regimens

What are the criteria for evaluating propo ed prophylactic and therapeutic regimens? The critical and decisive criteria are not the effects of a given regimen on symptoms weight plasma cholesterol or lipoprotein levels angina pectoris and the like These unfortunately are not adequate reliable criteria to judge efficacy of prophylaxis or therapy The essential problem is one of halting or at least retarding the progression of the basic atherosclerotic disease—or even reversing the process in whole or in part—with a resultant postponement or elimination of clinical episodes The only reliable criteria therefore are effects on occurrence and recurrence of clinical episodes of atherosclerotic disease (coronary cerebral and others) and above all effects on survival as measured by the duration of life

If these are the decisive meaningful criteria then many of the currently proposed approaches to prophylaxis and therapy are *at this juncture* based on inference *e g* the inference that lowering serum cholesterol may be effective in mitigating occurrence and recurrence of athero clerotic di ease For practically all of the proposed prophylactic and therapeutic regimens the validity of this inference has not yet been unequivocally demonstrated They are still experimental They are not yet components of the armamentarium of medical practice with proved and established status

One must not be misled by the influence of a proposed regimen on plasma cholesterol This is far more easily determined than effects on atherosclerotic disease The former involves studies taking only weeks

lipid and lipoprotein patterns In particular estrogens were found to increase plasma phospholipids, occasionally lower cholesterol reduce C/P ratios elevate α lipoprotein, and increase the ratios α/β lipoprotein and α/β lipoprotein cholesterol Comparisons of the plasma lipid lipoprotein patterns in normal males normal females and males with clinical coronary disease lent further support to the concept that estrogens may play a role in the 'immunity' of premenopausal women to coronary atherosclerosis

During these years four relevant studies were also published from clinico pathologic laboratories The first reported that young ovariecto mized women examined at autopsy several years after surgery, exhibited a significant loss of "immunity to coronary atherogenesis normally present in intact women of their age (713) The second study yielded similar findings In addition it reported that elderly males receiving prolonged high do age estrogen treatment for prostatic carcinoma, ex hibited significantly less coronary atherosclerosis than a matched control group receiving little or no hormone Finally it presented data indicating that women with breast carcinoma who presumably were hyperestrogenic also had less coronary disease than their controls It suggested that these changes might be attributable to specific anti atherogenic effects of estrogens (714) The third study presented data indicating that men and women with myocardial infarctions tended to excrete less biologically active estrogens and 17 ketosteroids than their controls (715) The fourth investigation confirmed that eunuchs manifested less coronary atherosclerosis than non castrate men (717 718) Correspondingly castrate men had higher serum α lipoprotein levels higher α/β lipopro tein ratios lower β lipoprotein and cholesterol concentrations These patterns resembled those seen in women or following estrogen adminis tration or androgen withdrawal Again it was suggested that these estrogen induced alterations in serum cholesterol lipid lipoprotein metab olism might be responsible for the relative freedom of the estrogen dominated eunuch from coronary atherosclerosis

In concluding this section on hormonal and other endogenous factors and atherosclerosis one general point merits re emphasis These studies dealt with the effects on the organism of an *interplay between potentially atherogenic diets and endogenous factors* This was true for investigations in both human beings and experimental animals Without a nutritionally induced potential for atherogenesis significant lesions were not observed irrespective of the endogenous factors operating in the organism

keeping it reduced is therefore, clearly established as beneficial to all persons subject to atherosclerosis It is something every physician should advocate The diet prescribed obviously should have adequate amounts of the essential nutrients

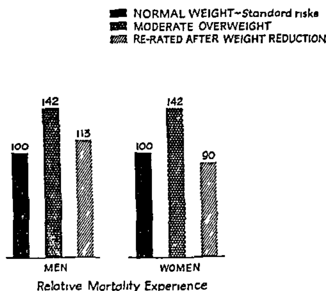


FIG 58 Shepard W P and Marks H H (285) Note that in the groups undergoing weight reduction relative death rates tended to be similar to those of the normal weight standard risk groups in contrast to the 4? per cent higher rates in the obese groups

2 *Low Fat Low-Cholesterol Diets* —Three reports have been published on the therapeutic effects of low fat low-cholesterol diets in patients with established coronary heart disease (366–368 372 373 722 723 *cf* also ref 724) * In the first of these two groups of patients with proved myocardial infarction were followed for 8 years (366) A low fat low cholesterol diet—containing approximately 1 600 calories daily 20 to 25 grams fat 50 to 70 mg cholesterol 225 grams carbohydrate 120 grams protein plus supplemental nutrients (Brewer s yeast and whole wheat germ)—was prescribed for one group of 50 subjects The other 50 continued to ingest their habitual diets The treated group experienced a significant weight loss occurring during the initial 3 years thereafter

*Several recent publications present detailed pract cal information on diversified pleasant low fat low-cholesterol diets (369 372–374 722 723)

or months the latter requires at least five years of study The former is an essential first step, but only a first step The latter is massive, expensive, difficult, and a long term undertaking, hence its comparative rarity More such are needed

C Precautions in Evaluating Prophylactic and Therapeutic Regimens

What are essential precautions in the evaluation of possible prophylactic and therapeutic regimens? The critical problem is one of control The number of subjects under investigation must be adequate to yield a statistically "clean" answer at the medically anticipated level and in an anticipated time (e g a 50 to 75 to 90 per cent reduction in 4 year mortality rate) A matched placebo group—set up on a "double blind" basis—is virtually an inevitable and vital necessity "Matched" should mean by age sex race ethnic origin occupation income socioeconomic status, place of residence by height weight body build In therapeutic studies, "matched" should mean by number time location severity of episodes of clinical atherosclerotic disease diagnosed according to uniform accepted criteria "Matched" should further mean by cholesterol lipid lipoprotein levels by other diseases related or unrelated particularly hypertension other heart or cerebral diseases renal or thyroid or hepatic diseases diabetes mellitus "Matched" should mean optimal uniformity in procedures for both treated and placebo groups e g apparently similar approaches to dietary advice to prescription of medication visits to the physician adjuvant therapy and other procedures

A most important additional precaution is the institution of adequate measures to assess adherence Investigators should have accurate objective criteria for evaluating whether subjects are taking pills sticking to diets and so forth Finally satisfactory methods are essential for follow up of cases who drop out of the study ("lost" patients) and for determination of cause of death (with autopsy verification insofar as possible) These complex precautions are not easily effectuated Several studies recently published fall short of the mark in one or another of these aspects

D Specific Proposed Prophylactic and/or Therapeutic Regimens

Let us evaluate specific prophylactic and therapeutic regimens currently under investigation on the foregoing basis With but a single exception no adequate long term prophylactic studies of any kind have been published

1 *Obesity Correction* —The exception is a recent report from life insurance sources on the prophylactic effects of correcting obesity The data indicate that grossly obese individuals—with much higher risks of death due to coronary disease—experience a definite lowering of risk following weight reduction (Fig 58) (284 285) Reducing weight and

farction recurrence rate and fatality rate (2 6 per cent *vs* 10 per cent mortality rate due to recurrent myocardial infarction) This difference certainly appears significant However, this paper presumably a preliminary report, is brief and sketchy Final judgment must await publication of the detailed data

The third report involved a follow up of 175 patients for a period of from 36 to 72 months (368) All patients were originally put on a low fat, low cholesterol diet Of these 26 failed to respond with a reduction of cholesterolemia, and 39 others after a brief period failed to adhere to the diet These two groups were used as the controls In the 110 patients responding to the diet, the serum cholesterol level fell from a mean control value of 329 mg % to a mean treatment concentration of 270 In every one cholesterol fell more than 10 per cent, and the cholesterol/phospholipid ratio fell at least 20 per cent In this treated group only 10 deaths occurred during the mean treatment period of 50 months (mortality rate 11 per cent) in the last 11 months of therapy only one patient of 98 died In contrast the mortality rates in the other two groups were 31 per cent (8 of 26 patients) and 33 per cent (12 of 39 patients) during 51 and 53 months of observation respectively The design of this study, particularly the manner of establishing the control group is open to criticism, yet the results are suggestive

Obviously, the question of the value of such low fat diets is unsettled Additional work along these lines is needed in view of certain possible limitations in the design of these studies judging from the published reports However the practicing physician would do well to consider this type of diet in dealing with the prevention and retardation of atherosclerosis This is discussed in more detail below

3 *Unsaturated Oils* —As already indicated particular attention has focussed during the last year or two on the effects of unsaturated vegetable and marine oils on cholesterolemia and β lipoproteinemia As yet no reports have been published on the long term prophylactic and/or therapeutic effects of these oils However the practicing physician will be well advised to consider the use of unsaturated fats in lieu of saturated ones as part of his armamentarium in the handling of atherosclerosis The substitution of unsaturated for saturated fats in diets kept moderate or low in total fats is warranted in our present state of knowledge This can be accomplished by proper selection of foods (see below) It is not warranted today merely to add unsaturated fats as supplements—in the form of corn oil safflower oil and their like The *total fat and saturated fat content should be lowered* and overweight avoided Specific dietary recommendations are given below

4 *Sitosterols* —Another specific approach to therapy in recent years involves plant sterols Extensive studies were undertaken on the effects of sitosterols in man With few exceptions ingestion of large doses of plant sterols induced significant sustained reductions in serum choles

weight remained stable Serum total lipids cholesterol and neutral fats declined markedly Survival rates were significantly better in the treated group, compared with the controls, particularly at the 8 year interval (Fig 59) However examination of this paper gives no clearcut indication that the two groups of "unselected patients" were in fact matched by age and sex for example Hence the validity of these apparently impressive findings cannot be unequivocally accepted

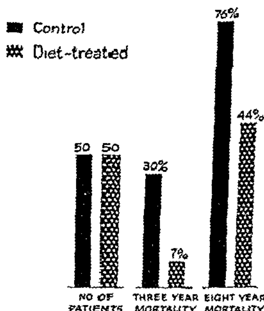


FIG 59 Morrison L M (366) The two groups were made up of unselected patients with proved myocardial infarction who survived their initial attack and whose condition was uncomplicated by other diseases such as hypertension diabetes mellitus nephritis thyroid disease xanthomatosis (366) No data are given which permit assessment of the comparability of the two groups on an age sex basis Note the lower mortality rates at both 3 and 8 years in the group on low fat low cholesterol dietary treatment

The second report presented a 4 year follow up of 280 patients with previous myocardial infarction of whom 155 presumably adhered to a low fat low cholesterol regimen (50 grams fat 200 mgm cholesterol daily) (367) The two groups dieters and non dieters were of similar age They had comparable β lipoprotein levels at the onset of the study The therapeutic diet effected a significant decline in these values whereas no change occurred in the untreated group With an average follow up period of about 4 years the treated group had a significantly lower in

people free of clinically manifest atherosclerotic disease It should be considered only in those who have had myocardial infarction or a cerebro vascular accident, especially when there is evidence of repeated thrombo embolism Close observation of all patients on long term anticoagulant therapy, with frequent determinations of prothrombin time, is of course absolutely essential to avoid potentially dangerous complications

Four year mortality in cases of Myocardial Infarction treated with long-term anticoagulants

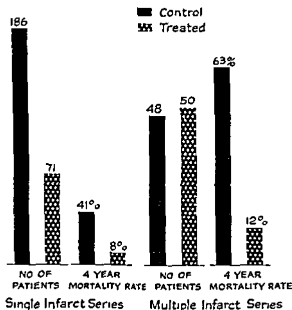


FIG 60 Keyes J W Drake E H and Smith F J (75?) Although the statistical methods for evaluation of survival time employed in this study seem predicated on comparability of control and treated groups the published report presents no data on age sex previous medical history (other diseases) and so forth Therefore comparability of the groups cannot be definitively evaluated

7 *Antihypertensives* —Hypertension markedly increases the risk of atherosclerotic disease particularly in the presence of a derangement in cholesterol lipid lipoprotein metabolism

With recent progress in drug therapy for the hypertensive state it is becoming possible to assess the effects of successful blood pressure reduction on development and progression of atherosclerotic disease Thus far only limited—but encouraging—data have been presented (772) On this basis antihypertensive drug therapy or even surgical symphathec tomy is to be considered seriously as a means of helping retard athero sclerosis in any patient who has clinical manifestations of coronary or

terol (725–740) Recent studies indicate that marked lowering of cholesterol levels may be effected by combining plant sterols and dietary changes (362, 363, 403, 741) Preliminary data have been presented suggesting favorable long term therapeutic effects of sitosterols in patients with clinical atherosclerotic disease (742, 743) But definitive evaluation of this proposed therapeutic regimen must await more detailed reports

Results similar to those obtained with sitosterols have been reported in studies on man utilizing a brain extract (572, 573 575 576) Here again, no long term evaluations have appeared in the literature This method is therefore not yet suitable for the practicing physician

5 *Lipotropic Factors* —Negative results have been obtained in most studies in man (as well as experimental animals) with lipotropic factors—choline inositol lecithins, lipocaic and other pancreatic preparations methionine and other factors (1 12–14) With few exceptions no cholesterolemia reducing effects have been reported Further no data have been published on long term prophylactic or therapeutic effects The status of tocopherols (vitamin E) is similar

Recent reports suggest that significant results in lowering serum cholesterol may be achieved in man with large doses of nicotinic acid or pyridoxine with a dietary regimen incorporating linolenic acid pyridoxine and chelating agents and with several non biological chemicals (538 586–594, 741 744–748) However none of these has been studied in long term investigations and none of these are recommended for general clinical use

6 *Anticoagulants* —Research on the possible efficacy of long term anticoagulant therapy has advanced further (749–764) Suggestive positive results—reduction in recurrences and prolongation of life in patients with coronary heart disease—were reported in several different studies using chiefly dicumarol at dosage levels yielding sustained prolongation of prothrombin times (Fig 60) However a major cooperative British study has not yet revealed definitive results (765) Marked reduction in mortality—4 per cent cardiovascular renal mortality rate in the treated group *vs* 18 per cent in the control—was also reported in a series of cases of myocardial infarction treated intermittently with parenteral heparin (750) The doses utilized (200 mg twice weekly) did not produce sustained therapeutic anticoagulant levels On the other hand most studies with heparin for the treatment of angina pectoris have yielded negative results (766–771)

However detailed review of the papers on long term anticoagulant therapy raises questions as to the adequacy of controls in some of these investigations With this reservation it may be generally stated that the overall results are sufficiently suggestive particularly with dicumarol to justify its consideration for long term therapy in some cases pending the final report of the more adequately designed British study Anticoagulant therapy, at present, has no applicability prophylactically in

considerable data have been presented particularly from the Joslin Clinic indicating that effective control of diabetes mellitus results in significantly fewer vascular complications It would seem valid that there may be a risk of aggravating athero clerosis by attempts at very rigid control of the diabetic state, particularly with the use of too much insulin The practicing physician would be well advised therefore, not to enforce too rigid diabetic control to avoid unnecessarily large doses of insulin with the inevitably excessive fluctuation of blood sugar level, and to use the apparently more physiologic oral insulins wherever possible

9 *Thyroid Hormone* —Recent studies have re opened the question of the value of thyroid hormone in the prophylaxis and therapy of athero sclerotic disease (1, 8 12–14 645 688) This problem has a long history It was recently reported that marked sustained reduction in human serum cholesterol and β lipoprotein concentrations can be effected by administration of large doses of desiccated thyroid (3 4, 5 or more grains daily) (Fig 61) (774, 775) These lowered levels were successfully main tained for many months with continuous hormone exhibition Obviously necessary precautions are indicated in utilizing this medication in patients with manifest clinical coronary disease and resultant limited myocardial reserve Again, the fact must be noted that no data are available on the long term prophylactic or therapeutic effects of thyroid hormone

/ Possible utility of thyroid hormone as a specific definitive method of prophylaxis and therapy for atherosclerotic disease does not negate the possible value of thyroid ablation as a late palliative measure in selected cases of intractable angina pectoris (776) This applies also to the use of thiouracil and I^{131} However the evidence available in our opinion points to a real hazard associated with all procedures which decrease thyroid function below normal—namely the potential of accelerating atherosclerosis Proper diet control could lessen this hazard A balance must be struck between the possible benefits of thyroidectomy thiouracil and I^{131} on anginal symptoms—when they are debilitating—and the pos sible harm arising from acceleration of atherosclerosis Obviously there fore the anginal syndrome must be sufficiently severe in the patient before these thyroid depressing procedures are contemplated

10 *Estrogens* —The rationale for the use of estrogens in prophylaxis and therapy was summarized above To date no data have been pre sented concerning the possible prophylactic utility of estrogens in pre- venting development of clinical atherosclerotic disease in postmenopausal women However if uterine bleeding can be controlled there is no harm in their use—provided small doses are employed It would appear un likely that estrogens will find any use in the prophylaxis of atherosclerotic diseases in males unless future results should demonstrate an influence in small doses producing no side effects—or if an estrogen is found with proved antiatherogenic potency but no feminizing effect No such estro gen is yet available

cerebrovascular atherosclerosis Best of all antihypertensive procedures and diet regulation should be combined The use of antihypertensive drugs—particularly the more powerful depressors, *e g* ganglionic blocking agents in—benign hypertension, before such clinical manifestations have appeared, has not been clearly established However their possible employment when the risk of *clinically manifest atherosclerosis is great* (see below) should be seriously considered

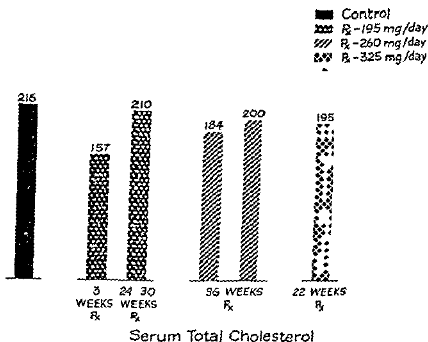


Fig 61 Strisower B Gofman J W Galiom E F Rubinger J H Pouteau J and Gurvich P (775) Note that the lower dosages of desiccated thyroid reduced serum cholesterol level initially but that it rose latterly With a dosage of 325 mg /patient/day moderate sustained decrease of cholesterolemia was apparently achieved

8 *Diabetes Control* The complex and controversial problem of control in diabetics and the development of vascular complications has been discussed previously (*cf* 1 12–14 773) Diabetes mellitus is a condition which indicates the use of diets restricted in total fat and cholesterol low in saturated fat adequate in essential fatty acids minerals vitamins proteins With such a diet the marked tendency of diabetics to manifest hypercholesterolemic hyperlipemia can often be counteracted and the integrity of the vasculature maximally protected It is also true that

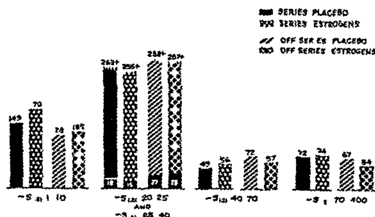


FIG 63 Stamler J Pick R Katz L N Kaplan B and Pick A (721) Note that the 4 groups had similar control serum lipoprotein levels

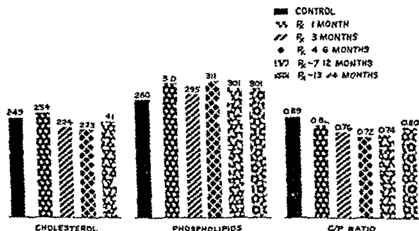


FIG 64 Stamler J Pick R Katz L N Kaplan B and Pick A (721) Note that the effects of estrogens (10 0 mg /patient/day) on serum lipid levels tended to persist for as long as 2 years

Estrogen therapy in man was the area of activity which our group selected because of our work with estrogens in animals In 1952, a long term evaluation was begun of estrogen therapy in middle aged males with previous myocardial infarction * This study was recently described in comprehensive reports (645, 721, 777) Every effort was made to take necessary precautions particularly proper matching of placebo and treated groups, as outlined above All patients are men under age 50 with proved coronary disease The groups are in fact matched closely —

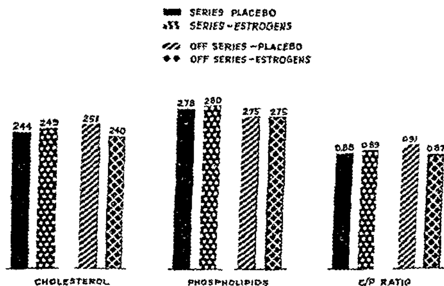
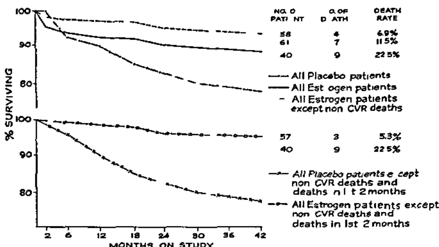


FIG 62 Stamler J Pick R Katz L N Kaplan B and Pick A (721) Note that the 4 groups in this long term therapeutic evaluation had similar control serum lipid levels

by age, ethnic origin occupation disease history height weight pre treatment plasma cholesterol lipid lipoprotein levels (Figs 62 63 and 64) Since June 1954 the standard maintenance dosage has been 10 mg of conjugated equine estrogens daily by mouth It is our current practice to arrive at this dosage level gradually in a stepwise fashion over months beginning with 1 25 mg then increasing to 2 5 4 0 and then 10 mg

The anticipated effects on serum lipids lipoproteins have been consistently observed *i e* an increase in α lipoprotein and phospholipids with a

* It was recently reported that estrogens are ineffective in the treatment of intermittent claudication and angina pectoris (778 779) On the other hand a preliminary report suggests favorable results with prolonged low-dosage estrogen therapy in idiopathic hyperlipemia and hypercholesterolemia (780)



	Sexes %	Risk % G			No with ...	No with Diabetes / Hypertension	Age / Infarct	Serum Cholesterol / ...	Height / Weight	No started on low dosage on 10 mg	Total No lost patients /	Total No of Deaths and %	No of non-CV deaths %	No CVR deaths during 1st 2mo. R %	No of Val deaths %
PLACEBO ½ Rs.	58		30		7		4	56 90		o		9		0	
ESTROGE ½ Yrs.		64	26	10	10		59	24						2	5

FIG 66 Stamler J Pick R Katz L N Kaplan B and Pick A (721) The total number of patients under observation for as long as 3½ years were 40 and 61 in the placebo and estrogen treated groups respectively Data on the comparability of the two groups are summarized in the table (*cf* text and ref 721) The patients were divided into good (G) poor (P) and unknown (U) risk based on the presence or absence of complications during the acute episode of myocardial infarction all patients with more than one infarction prior to the onset of the study were classified as poor risk There were no non-cardiovascular renal deaths in the placebo group hence the upper graph presents only 3 curves of survival There were 3 non-cardiovascular renal deaths in the estrogen treated group the survival curve for the estrogen treated patients excluding these 3 patients (a total of 58 pat ents) is the upper curve in the upper graph The number immediately to the right of the survival curve is the number of patients represented on the given curve The lower graph plots the survival curve for valid deaths i e cardiovascular renal deaths occurring after 2 months of medication had transpired There were no non-card ovascular renal deaths and no deaths during the first 2 months in the placebo group hence the curve plots the data for the entire group of 40 patients There were 3 non cardiovascular renal deaths after and 1 cardiovascular renal death during the first 2 months of drug administration in the estrogen treated group hence the survival curve for the estrogen treated patients in the lower graph excludes these 4 cases (leaving a total of 57 patients) Although these data indicate that estrogen therapy may be effecting a better prognosis for urvival the size of the groups followed for as long as 3½ years is too small to yield a statistically s gnificant clearcut result A longer period of follow up is essential to evaluate whether estrogens are or are not efficacious in the therapy of coronary heart disease in middle aged males

tendency for cholesterol to fall (Figs 64 to 66) (1, 4 5, 12–14, 645, 646, 704–719, 721) Hence, the ratios β/α lipoprotein and cholesterol/phospholipids are lowered These effects have been maintained for at least three, and as many as four years of treatment The α lipoprotein level—together with signs of gynecomastia—is therefore utilized as a reliable objective criterion of patient adherence to the estrogen regimen

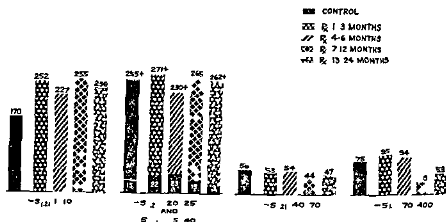


FIG 65 Stamler J Pick R Katz L N Kaplan B and Pick A (721) Note that the estrogen induced increase in —S 1–10 (α)lipoprotein levels tended to persist over as long as 2 years Similar data were obtained for an additional third year as of April 1957 (777)

As of March 1, 1958 276 patients had been brought under study, with the cooperation of several Veterans Administration hospitals throughout the Middle West An approximate 27 per cent attrition (drop out of patients) has occurred in the estrogen treated group compared to 19 per cent in the placebo group a difference attributable to the side effects of the hormone gynecomastia depression of libido and potency However these have certainly not been insurmountable problems On the dosage of 10 mg of the conjugated equine estrogens toxic effects (as distinguished from side effects)—*e g* nausea lassitude malaise diarrhea— have been minimal With respect to effects on recurrence rates of myocardial infarction and on survival, the data to date indicate the following trends While the overall rate of recurrence of myocardial infarction is similar in the two groups, the survival rate is higher in the treated group under observation for over 3 years (Fig 66) These differences are not at the level of statistical significance A longer period of follow up is essential We are therefore, not yet prepared to advocate use of estrogens routinely

of these actuarial predictions of risk will be false positives and false negatives respectively However, these "errors are of minor importance, reckoned against the ability to identify high risk individuals—with the consequent possibility of successful prophylactic intervention

Recent investigations are making it possible to estimate the scope of this problem of high risk individuals in specific quantitative terms Based on the data of the Framingham Heart Study (Fig 18), for example, it can be roughly estimated that a low risk middle aged male—normal in weight blood pressure and serum cholesterol—has 1 chance in 25 of

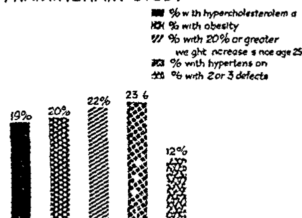


FIG 67 Dawber T R Moore F E and Mann G V (209) Note the extent to which these defects individually and in combination are present in the middle aged male population of Framingham Massachusetts

developing clinical coronary heart disease during the 45 to 64 age period In contrast a middle aged male with two or three abnormalities (obesity hypercholesterolemia hypertension) stands almost 1 chance in 2 These are very different risks

About 1 of every 8 middle aged American males falls into this high risk category (Fig 67) (209) When it is further recognized that 20 to 30 per cent of first attacks of myocardial infarction are fatal within the first few weeks the serious nature of the high risk situation is even more starkly apparent Is it not extremely valuable—for both patients and physicians—to be able to identify these high risk individuals in order to attempt to do something for them prophylactically?

In bad risk subjects can risk be prophylactically reduced several fold by correcting defects? It is known that these defects are amenable to

E Overall Evaluation

It is evident that the research activity of the last decade has led to several specific approaches, particularly to definitive therapy of clinical coronary heart disease However, for each of these approaches, unequivocal proof is not yet available concerning their efficacy Only the work in the next decade can complete this complex task of evaluation However some suggestions—as distinct from scientifically clear proof—have been derived and serve as the basis for certain tentative recommendations we have made above for the physician who is in practice Time alone will tell how sound they are

F An Interim Approach to Prophylaxis for High Risk Persons, and to Therapy

Throughout the foregoing discussion the key role of diet has been emphasized Obviously, routine therapy other than this is not yielding satisfactory results (781–784) There is room for improvement This conclusion in no way gainsays the importance of such established constituents of the therapeutic armamentarium as indicated medications and specific hygienic admonitions—*e g* reasonable schedules of work relaxation recreation and rest avoidance of tension frustration, stress over exertion fatigue undue competitiveness, prescription of appropriate physical exercise to maintain physical fitness and the like (see below) These recommendations continue to be of fundamental importance even as the medical profession goes beyond them to employ the more definitive therapeutic approaches The cornerstone of modern therapy for patients with coronary disease today seems to be an increasingly scientific dietary prescription aimed at correcting the nutritional metabolic derangements intensifying atherogenesis This is obviously of value for the person with clinical manifestations of coronary and cerebrovascular atherosclerosis It is valuable also for persons with a genetic handicap as regards atherosclerosis

For persons not yet victimized by clinical coronary disease it is also widely agreed among most investigators (6 195 372 373) that one sizable sector of the American population particularly needs prophylactic advice from the medical profession *i e* the middle aged male group with an inordinately high risk of developing clinical coronary heart disease This is the group with two or more derangements—obesity hypercholesterolemia hypertension renal damage diabetes hypothyroidism heavy smoking and/or a poor family history

While it is perfectly correct that no one can definitively predict whether a given person will or will not develop clinical coronary heart disease in the next year or two long term prognostic predictions of the actuarial type—predictions of risk—can be made Inevitably a small percentage

through utilization of vegetable oils, *e g*, corn oil As one important measure towards this end, the ordinary bacon eggs-buttered toast creamed coffee breakfasts—with their huge intake of saturated fats, calories and cholesterol—should become the exception and not the rule They should be largely superceded by breakfasts made up of fruits, whole grain cereals skim milk (enriched with nonfat dry milk solids), waffles or wheat cakes (made with enriched white flour and prepared with vegetable oil and skim milk), and spreads of honey, jam or marmalade used in moderation on whole grain or enriched breads

5 At other meals, the use of meats in moderation—preferably lean—prepared by broiling rotisserieing, boiling, steaming roasting with trimming of visible fat and avoidance of fat laden gravies and sauces Meat tenderizers may be used for flavoring—as can relishes and spices The utilization of poultry and sea foods in quantity prepared according to the foregoing recommendations The ample intake of vegetables and fruits The minimal use of highly processed refined foodstuffs having a low ratio of nutrients to calories These measures, in addition to the other objectives they achieve will insure the ingestion of a high protein diet

There is no doubt that this diet should be prescribed for every person who has had one or more clinical episodes of atherosclerotic disease such as angina pectoris myocardial infarction, certain forms of cerebral vascular diseases (those due to atherosclerosis) and atherosclerotic peripheral vascular disease It would seem logical to us that the above diet should also be followed by the following groups of persons—all of whom are subjects with a high risk of developing clinical atherosclerosis

1 Those who are obese on a typical American diet

2 Those who have a hypercholesterolemia over 260 or 275 mg per cent

3 Those who are hypertensive have diabetes mellitus or have renal damage (provided there is no specific contraindication in any particular patient)

4 Those who have a poor genetic history *i e* a familial predilection for clinical atherosclerosis in middle age

Such a program we feel convinced will reduce clinical atherosclerosis in this country to a significant extent within 5 years However this remains to be proven

This dietary regimen at first requires constant attention and adjustment on the part of the physician During this time the physician can combine it with simple and sound advice on a way of life for his patient who is approaching the second half of his life Emphasis should be on moderation—in his vocation and avocation There should be a reduction of excessive competition, acceptance of one s limitation and pride in what one has accomplished—without too much smugness The physician should preach a habit of not so much ambition as to make the person constantly unhappy nor too little to make him bored—and boring The

correction in whole or in part by relatively simple diet therapy It is not yet known definitively whether coronary heart disease can be significantly lowered thereby, *although the findings of the life insurance companies on* the positive results of correcting obesity are highly suggestive in this regard (Fig 58)

There is widespread agreement among investigators on the individualized prescription of reasonable, moderate, safe, palatable dietary correction in high risk patients, particularly those with obesity, hypercholesterolemia, hypertension, renal damage, diabetes, poor family history, and other factors (6, 195, 372, 373, 720)

G Specific Recommendations

Recommendations for prophylaxis should be virtually without danger of any type—biological sociological or psychological For this reason—and because the accumulated evidence strongly suggests that the best results are likely to be achieved with *dietary* prophylaxis (coupled with a good overall hygienic regimen including regular physical exercise)—our general recommendations focus on this approach

Every effort should be made to advise prophylactic dietary corrections that are simple moderate familiar and feasible The average high risk person should not be enjoined to abandon the pleasures of eating Rather, he should be encouraged to graduate to a modified appetizing cuisine including a wide enough variety of palatable foods to allow even the gourmet ample play for his proclivities Stringent dietary restrictions *(and related adjuvant measures) should be undertaken only when* absolutely necessary *i e* when moderate measures fail to elicit a reduction in weight, cholesterolemia blood pressure

The general objective then is to correct the imbalances in the American diet cutting down on excesses and overcoming inadequacies This approach calls for the following simple safe reasonable, nutritional recommendations

1 The curtailment of the culinary custom of adding large amounts of fats, particularly saturated fats to foods the avoidance of frying and deep fat frying of preparing salads with cheese or sour cream dressings, and of putting butter margarine or cream on vegetables

2 For dessert, adherence to the French tradition of serving fruit, instead of the American routine of pies, cakes, ice cream and other similar desserts

3 The correction of obesity if present by reducing total caloric intake, total fat intake and ingestion of empty calories' from refined carbohydrates processed fats spirits and so forth

4 The reduction of fat intake from the present 40 to 60 per cent of total calories down to *20 to 25 per cent Along with this,* the accomplishment of an increase in the ratio of unsaturated fats to saturated fats—

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patient should run his job, not have the job run him He should have peace of mind and plenty of physical exercise to overcome our civilization's hectic pace and sedentary trend Frustrations should be kept at a minimum, competition—while useful as a driving force—should not become too much of a compulsion In short, the high risk individual must be reminded that it is not how high he (or she) climbs that is harmful, but rather how fast and over how many obstacles Physicians can help high risk patients with general advice of this sort, if they are willing to spend enough time with their patients over their troublesome day by day problems The ability of a patient to unburden himself to a sympathetic and knowledgeable physician is obviously beneficial psychologically—and doubtlessly medically This role, we believe, should be assumed by more physicians

As more and more knowledge comes to the fore, generalities in medical advice will become more specific There is great need, in our opinion to study more intensively the role of the psychological and emotional make up of the individual, and of physical and psychical stresses in the atherosclerotic process

Finally our attention has been on the etiology, prophylaxis and treatment of the basic process of atherosclerosis There is adequate coverage of the handling of sequelæ and clinical manifestations in other books monographs and reports However we must stress that if atherosclerosis is absent, its complications and sequelæ cannot occur!

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